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Inconsistent outcomes of transcranial direct current stimulation may originate from anatomical differences among individuals: Electric field simulation using individual MRI data

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HIGHLIGHTS

- The relationship between conduction current and the behavioral outcomes after tDCS was studied.
- The current density at DLPFC was related with working memory performance after tDCS.
- Inconsistent outcomes of tDCS may originate from anatomical differences among individuals.

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ABSTRACT

Transcranial direct current stimulation (tDCS) is a neuromodulation protocol that can facilitate or inhibit cortical excitability in particular areas of the brain. Although recent studies have reported that tDCS can successfully modulate the excitability of various brain sites, outcomes of tDCS were not consistent between subjects even when identical stimulation protocols were applied. Thus far, however, no studies have clearly verified the main cause of this individual variability. In this study, the main hypothesis was that individual variability in tDCS effects might be partly explained by anatomical differences among subjects. To verify our hypothesis, we investigated the relationship between the behavioral outcomes of a verbal working memory (WM) task and current density values at the dorsolateral prefrontal cortex (DLPFC) simulated using the finite element method (FEM). A 3-back verbal working memory task experiment was conducted in 17 healthy subjects before and after tDCS with cathode and anode electrodes located at the right supraorbital and F3 locations, respectively. The results showed that participants who showed evidence of enhanced WM task performance after tDCS had a significantly larger current density at the DLPFC than other participants, suggesting that inconsistent behavioral outcomes of tDCS might be partly due to individual anatomical differences.

1. Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive neuromodulation technique, which can modulate cortical excitability by delivering low-intensity direct current (DC) though the scalp [4]. The applied DC modulates the membrane potential of neurons and leads to changes in the neuronal firing rate [20]. The dependence of the tDCS after-effect on the polarity of the applied current has been thoroughly investigated and studies have shown that anodal and cathodal stimulation facilitates and inhibits cortical excitability, respectively [21]. Excitability changes in local cortical neurons can consequently induce cognitive, psychological, or physiological changes in the human brain. For instance, it has been suggested that working memory (WM) performance can be modulated by stimulating the left dorsolateral prefrontal cortex (DLPFC) [8]. Although individual differences in tDCS outcomes have been noted, anodal tDCS applied to the left DLPFC has shown statistically significant enhancement of WM performance not only in healthy controls but also in patients with stroke or Parkinson's disease [3,14,24].

However, although there are studies reporting that tDCS outcomes are affected by various factors such as stimulation duration,

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electrode size, and injection current strength, no previous studies systematically investigated why there exist considerable individual differences in tDCS outcomes under identical stimulation conditions. For instance, although a study by Boggio et al. [3] showed gradual improvement in WM performance with respect to the incremental changes of the injection current strength, they did not fully explain why some participants showed more improvement with less stimulation current or why some participants did not show any differences with respect to different current levels.

The main hypothesis of our study is that individual differences in tDCS outcomes might be partly due to differences in individual anatomy, such as cortical folding structures, skull thickness, and brain shape. Recently, many researchers have adopted individualized stimulation approaches using electric field analysis based on the finite element method (FEM) to determine optimal stimulation parameters including configuration, sizes, and locations of scalp electrodes as well as current strength [2,7,9,18,19,25]. However, to the best of our knowledge, no previous studies have quantitatively evaluated the relationships between behavioral outcomes and conduction currents delivered to target brain areas.

In this study, we investigated the relationship between the current density of DLPFC generated by tDCS and changes in individual WM performance using electric field analyses with individual MRI data. A total of 17 healthy subjects took part in the 3-back verbal WM task experiment before and after the 20-min transcranial DC (tDC) stimulation. Subjects were classified into two groups based on whether they showed enhanced WM performance or not. The individual current density values at the DLPFC were evaluated using FEM with individual MRI. Average current density values of the two groups were then statistically compared to verify our hypothesis, which stated that WM performance changes due to tDCS might be associated with the stimulation current delivered to the DLPFC, which is dependent only on individual anatomical differences.

2. Materials and methods

2.1. Subjects

A total of 25 healthy subjects with a mean age of 22.4 ± 1.4 years (18 males and 7 females) initially took part in the experiment. All subjects were healthy and did not take any medications or drugs. Participants had no history of neurological, psychiatric or other diseases that could affect the experimental results. There were two participants excluded from the study because of low MRI quality. All participants signed a written informed consent approved by the Institutional Review Board (IRB) of Samsung Medical Center prior to participation in the study.

2.2. Experimental procedure

All participants performed a 3-back verbal working memory task before and after tDCS. The 3-back verbal working memory task consisted of 28 Korean syllabuses presented randomly during each trial. Presentation time of each trials was set to 1000 ms and inter-stimuli time was set to 200 ms. The subjects were instructed to press a button when a syllabus matched the one presented three times prior to the current one (Fig. 1a). Reaction time was recorded simultaneously using E-prime software (Psychology Software Tools, PA, USA). Before the experiments, all the participants were provided with enough pre-training sessions to be accustomed to the 3-back WM task. Based on the results of the initial 3-back WM task experiment, we excluded 6 subjects whose task performances (accuracy) were too high (above 90%) or too low (below 30%) to maintain homogeneity of the participants. Four subjects with high task performance were excluded because there was not enough room for their performance enhancement. On the other hand, two subjects with low task performance were excluded because it was thought that they did not actively engage in the task nor fully understand the task rules despite the sufficient pre-training sessions and our best explanation about the task protocols. The six subjects did not participate in further experiments, post-tDCS WM task and MR imaging.

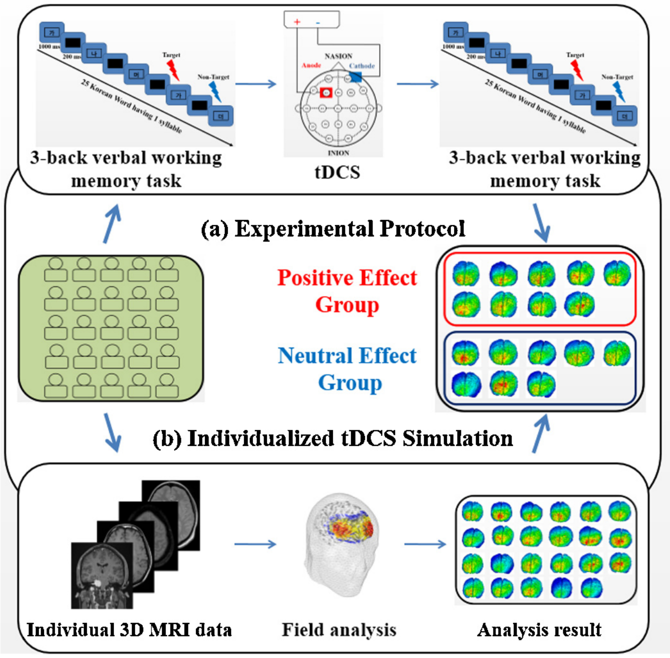

Fig. 1. Schematic illustration of the study protocol. (a) Participants were classified into two categories based on behavioral indices of the WM tasks: a group of individuals who showed a positive tDCS after-effect and the other group of individuals who did not show any significant enhancement in behavioral outcomes. (b) The current density distribution elicited by tDCS was evaluated using finite element analysis with individual MRI T1 data. Group comparison of current density values at the DLPFC was then performed.

Each subject underwent tDCS for 20-mins after performing the initial WM task. The anode and cathode electrodes were placed on F3 and right supraorbital region, respectively (see Fig. 2). The stimulation current (1.0 mA) was delivered to the brain using an Eldith DC-Stimulator (Neuroconn GmbH, Ilmenau, Germany) with 5 cm × 7 cm rectangular sponge electrode pads. After tDC stimulation, participants underwent another session of the 3-back verbal WM task with different syllabuses (Fig. 1a).

The 17 participants (13 males and 4 females; age: 22.2 ± 1.4 years) were divided into two groups, a positive-effect (PE) group and neutral-effect (NE) group according to the following three criteria:

(1) If the post-tDCS WM task performance (accuracy) was significantly enhanced compared to the pre-tDCS performance, they were categorized into the PE group.
(2) If the accuracy did “not significantly” increase but the reaction time of the post-tDCS decreased, they were also categorized into the PE group.
(3) The others, in whom conditions 1 and 2 could not be applied, were classified into the NE group.

According to the above criteria, nine participants were classified into the PE group and eight were categorized into the NE

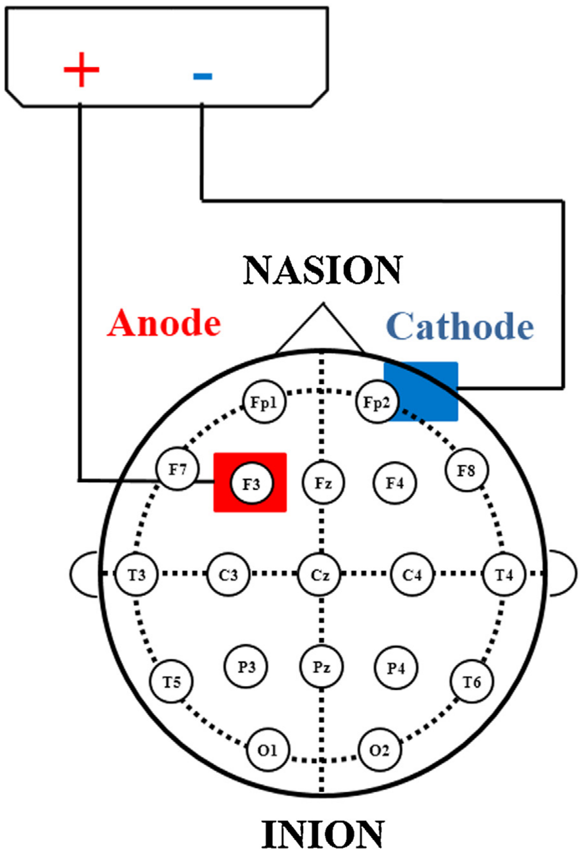

Fig. 2. Electrode locations used for tDC stimulation. 'Anode' denotes the electrode with positive potential and 'cathode' denotes the electrode with negative potential. In our experiment, the anode was located at F3 and the cathode was located in the supraorbital area.

group. Each participant's behavioral data are summarized in the Supplementary Table 1.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2014.01.054.

2.3. Analysis methods

MRI data were acquired from a commercial 3.0-T MR system (Philips Medical Systems, Andover, MA, USA) using gradient-echo EPI sequence (TR = 3000 ms, TE = 35 ms) with 1.719 mm × 1.719 mm resolution (FOV = 220 mm × 220 mm, thickness = 4 mm). Current density elicited by tDCS was computed using an FEM-based MATLAB toolbox, COMETS, developed by our group (http://www.cometstool.com, Fig. 1b). COMETS is a MATLAB toolbox that can analyze local electric fields generated by tDCS [16]. For accurate evaluation of the conduction current flowing inside the brain, finite element (FE) head models were constructed from individual MRI data. Each FE head model consisted of three areas - skin, skull, and cerebrospinal fluid (CSF)/cortex. The conductivity values for skin, skull, and CSF/brain were set to 0.22, 0.014, and 1.79 S/m, respectively [10]. For segmentation of MRI data, CURRY7 for Windows (Compumedics, Inc., Charlotte, NC, USA) was used.

The statistics package SPSS 18 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. We used both parametric and non-parametric statistics, Student's *t*-test and Wilcoxon-rank-sum test, under the assumption that larger stimulation current would be delivered to the DLPFC in the PE group than the NE group.

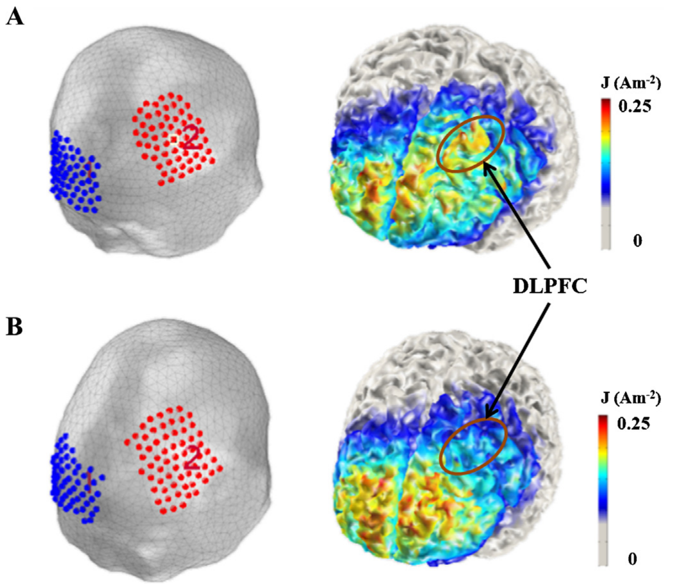

Fig. 3. Examples of individual current density maps of two subjects. (a) The cortical current density distribution of a participant (subject #3, PE group) and (b) that of another participant (subject #13, NE group).

3. Results

Fig. 3a shows an example of the current density map of a subject in the PE group and Fig. 3b shows that of a subject from the NE group. Despite the fact that both subjects were stimulated by tDCS using the same 10-20 electrode position (anode: F3; cathode: supraorbital), two current density maps showed distinct differences, especially around the DLPFC because of anatomical differences between subjects. Fig. 4a and b shows the scatter plots between current density at DLPFC and changes in accuracy and reaction time, respectively. Correlation between current density and accuracy change was not significant ($r = 0.248$, $p = 0.337$), but that between current density and reaction time change was marginally significant ($r = -0.447$, $p = 0.072$). There was no significant correlation between accuracy change and reaction time change ($r = 0.140$, $p = 0.592$) (Fig. 4c). In contrast, the current density at DLPFC showed significant positive correlation ($r = 0.665$, $p = 0.004$) with the transformed *z*-score (*z*-score = (*z*-score of accuracy change) - (*z*-score of reaction time change)), suggesting that the amount of current density delivered to DLPFC is closely related to the behavioral change after tDCS (Fig. 4d). The average current density values at the DLPFC were 7.045 ± 0.629 ($\times 10^{-2}$ A/m^2) for the PE group ($n = 9$) and 6.212 ± 0.935 ($\times 10^{-2}$ A/m^2) for the NE ($n = 8$) group (Fig. 5). The current density at the DLPFC during tDCS was significantly larger in the PE group than the NE group ($p = 0.0228$, one-tail independent t-test; $p = 0.0521$, one-tail Wilcoxon rank sum test), indicating that the effect of tDCS was dependent on the amount of the stimulation current delivered to the DLPFC, which mainly resulted from individual anatomical differences.

4. Discussion

Our results demonstrated that the cortical current density distributions due to tDCS were different even though the same electrode configuration (anode: F3; cathode: supraorbital) was applied to all subjects. Electric field analysis using individual MRI data showed relatively higher stimulation currents delivered to the DLPFC in individuals in the PE group compared to those in the NE group. Statistical analysis showed that the difference in current density

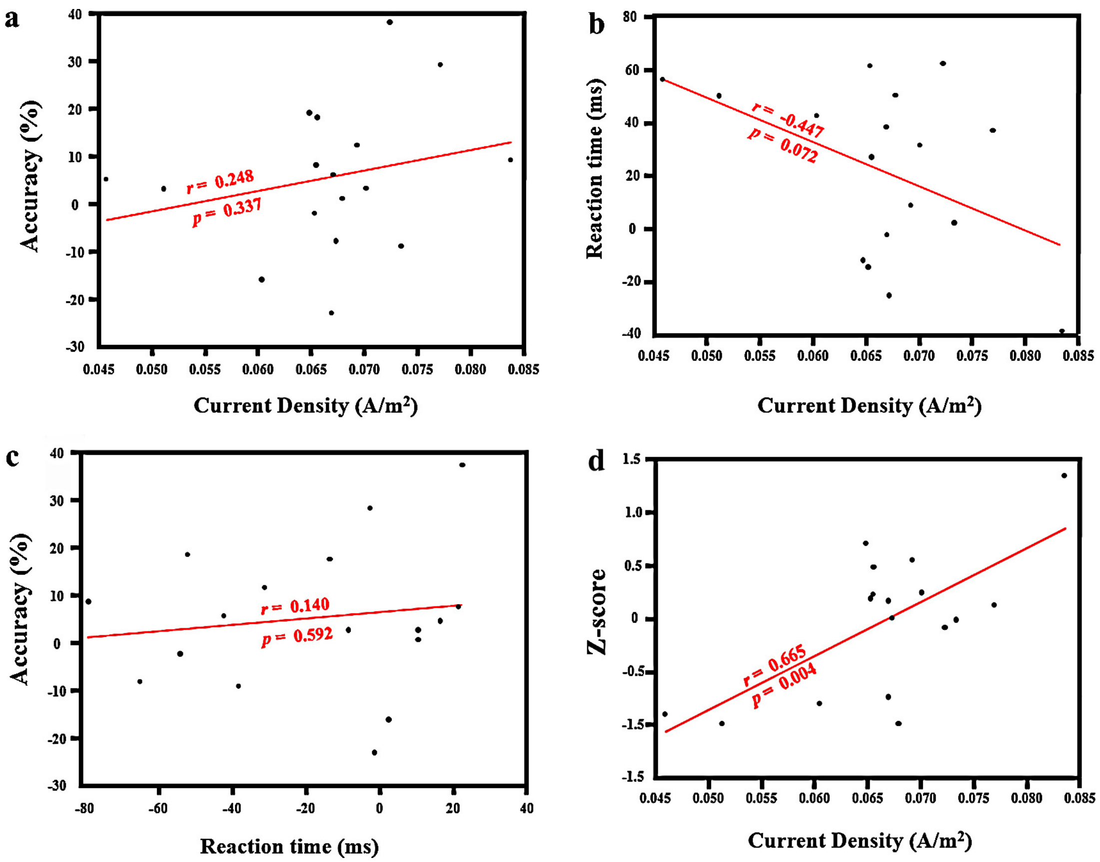

Fig. 4. Scatter plots of relationships between current density at DLPFC and behavioral factors: (a) relationship between current density and changes in accuracy, (b) relationship between current density and changes in reaction time, (c) relationship between accuracy change and reaction time change, and (d) relationship between current density and the transformed *z*-score (*z*-score = (*z*-score of accuracy change) − (*z*-score of reaction time change)).

at the DLPFC is related with behavioral outcomes of the DC stimulation. Therefore, our results suggest that behavioral outcomes of tDCS might be closely associated with individual anatomical differences, further demonstrating the necessity of individualized tDCS stimulation based on the electric field analysis.

Recent studies have shown that tDCS outcomes are mainly influenced by the tDCS current dose. Boggio et al. reported that patients with Parkinson's disease were successfully stimulated with a 2 mA injection current, but not with 1 mA current [3]. Iyer et al. also reported that subjects were not stimulated effectively with a 1 mA current but were successfully stimulated with a 2 mA current [13]. Based on these reports, some studies have attempted to increase the current density at a specific target brain area without increasing the total amount of injection current. Target brain areas could be more effectively stimulated by a ring-type multiple electrode configuration [6], by using a multiple array-type electrode configuration [17,22], or by directly adjusting electrode locations [11,12]. As mentioned previously, many recent studies on individualized stimulation based on realistic 3D field analysis have a common underlying assumption that determination of tDC stimulation parameters based on the electric field analysis would increase the current density delivered to the targeted brain area and thereby enhance tDCS outcomes. However, despite these studies, no previous studies provided any concrete evidence demonstrating that tDCS outcomes are influenced by differences in individual anatomy. To the best of our knowledge, the present study is the first report that attempted to systemically show the relationship between the current density at a specific target brain area and the behavioral outcomes after tDCS with a relatively large subject set. Our results suggested that individualized, customized, field-analysis-based tDC stimulation would potentially enhance the overall behavioral outcomes of tDCS.

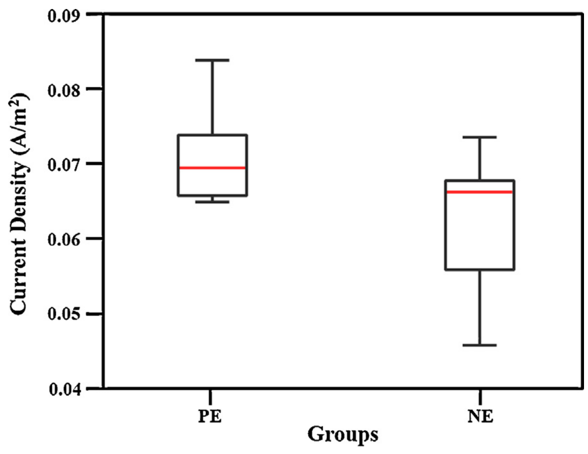

Fig. 5. Comparison of the current density value at the DLPFC elicited by tDCS (PE: positive effect group; NE: neutral effect group).

Berryhill and Jones reported that education rate may be one of the factors that can lead to differences in tDCS effects [1]. In their other study, they found that individuals with relatively higher initial WM task performance showed more improvements in task performance after tDCS [15]. Similar trends could be also observed in our results. The initial WM task accuracy of PE group was higher than that of NE group ($p = 0.0313$, independent *t*-test). However, our classification criteria were different from those of the previous studies in that we considered response time as the other important performance measure. For example, a subject 4 (in the supplementary Table 1) showed only slight increment of WM task accuracy, and thus could be categorized into the NE group if the accuracy was the only criterion. If that subject was categorized into the NE group, the statistical significance between two groups would be banished ($p = 0.1583$, independent *t*-test). Nevertheless, since it is still possible that the participants' initial WM task performances, which is irrelevant to current stimulation, might partly influence the tDCS outcomes, better-controlled experiments would be needed in future studies to completely exclude any potential baseline effects. In addition, it would be also an interesting future topic to investigate the relationship between morphological differences that are known to affect the WM task performance [5,23], and the stimulation current density at DLPFC.

There are some limitations in our study. We assumed the CSF and brain as a single tissue with an identical electrical conductivity, which might result in errors in the electric field analysis. This crude approximation was inevitable in our simulation study as the quality of MRI T1 images of some individuals was not good enough to clearly see the interface between the CSF and brain. This made it difficult to extract the boundary surface mesh between the two areas. The other limitation was that the number of subjects who participated in the study was not sufficient. Despite these limitations, our preliminary results are meaningful in that we demonstrated inconsistent outcomes of tDCS might be partly due to individual differences in brain anatomy. Further studies are needed in the future to confirm our findings with larger number of subjects. In addition, quantification of the relationship between various parameters associated with the brain morphology and the cortical current density would be an interesting topic that needs to be studied further.

5. Conclusion

In this study, we demonstrated that the conduction current density values at the DLPFC due to tDCS were significantly different between PE (positive-effect) and NE (neutral-effect) groups. This suggests that individual variability in behavioral outcome changes during the WM task after tDCS are associated with the current density values at the DLPFC. Since the current density at the DLPFC was dependent only on the anatomical structures of each individual in our simulation study, it can be concluded that the inconsistent tDCS outcomes might originate from differences in the anatomical structures among subjects. Our study also suggests that individualized field-analysis-based stimulation may be a promising solution to reduce individual variability of tDCS outcomes and thereby enhance the overall behavioral outcomes of tDCS.

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