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Use of functional near-infrared spectroscopy to evaluate the effects of anodal transcranial direct current stimulation on brain connectivity in motor-related cortex

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Abstract. Transcranial direct current stimulation (tDCS) is a noninvasive, safe and convenient neuro-modulatory technique in neurological rehabilitation, treatment, and other aspects of brain disorders. However, evaluating the effects of tDCS is still difficult. We aimed to evaluate the effects of tDCS using hemodynamic changes using functional near-infrared spectroscopy (fNIRS). Five healthy participants were employed and anodal tDCS was applied to the left motor-related cortex, with cathodes positioned on the right dorsolateral supraorbital area. fNIRS data were collected from the right motor-related area at the same time. Functional connectivity (FC) between intracortical regions was calculated between fNIRS channels using a minimum variance distortion-less response magnitude squared coherence (MVDR-MSC) method. The levels of Oxy-HbO change and the FC between channels during the prestimulation, stimulation, and poststimulation stages were compared. Results showed no significant level difference, but the FC measured by MVDR-MSC significantly decreased during tDCS compared with pre-tDCS and post-tDCS, although the FC difference between pre-tDCS and post-tDCS was not significant. We conclude that coherence calculated from resting state fNIRS may be a useful tool for evaluating the effects of anodal tDCS and optimizing parameters for tDCS application. [DOI: 10.1117/1.JBO.20.4.046007]

Keywords: tDCS; fNIRS; coherence; MVDR; brain connectivity; brain stimulation.

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1 Introduction

Noninvasive brain stimulation has become one of the major tools for facilitating neuroplasticity in humans, especially in patients with brain disorders.[1] These techniques, including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and epidural cortical stimulation, can modulate neural activities, and thus induce beneficial neuroplastic effects. Previous studies have shown that applying noninvasive brain stimulation can improve patients' ratings or performance in pain,[2] speech,[3] and motor control.[4,5] As one of these promising noninvasive brain stimulation techniques, tDCS can modulate cerebral excitability by applying a weak direct current.[6] Due to advantages including relatively low cost, ease of application and no reported risk of inducing seizures,[7] tDCS has been used as a clinical tool for the treatment of some brain disorders. Clinical studies have proved its usefulness in improving performance in poststroke motor rehabilitation and depression.[1,3,8]

A common approach for the assessment of tDCS effects is to analyze the behavioral data of subjects. However, the behavioral data are often influenced by many factors and cannot objectively reveal the underlying cortical neuronal activity. Another important tDCS evaluation approach is to measure changes in cortical excitability. One common way to detect the cortical changes caused by tDCS is to measure the blood oxygenation level-dependent signals using functional magnetic resonance imaging (fMRI). Many studies have shown that fMRI can detect the neuroplastic resting-state functional connectivity changes in motor cortex caused by tDCS.[9–12] Although fMRI has a high spatial resolution (in millimeters), its expense is relatively high. This limits the application of fMRI to the assessment of tDCS.

Recently, functional near-infrared spectroscopy (fNIRS) has been used in measuring brain activation. It measures the intensity changes in reflected infrared light caused by changes in the concentration of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (Hb).[13] These changes reflect the hemodynamic response to neural activities and neurovascular coupling. FNIRS is cheap, noninvasive, and portable. More importantly, fNIRS is optical, so there is no interference with the electrical currents of tDCS. FNIRS has been applied in various research studies, including those of cortical plasticity and resting-state functional connectivity.[14,15] Therefore, fNIRS could be a useful tool for investigating the effects of tDCS.

There have been a few studies using fNIRS to detect the effects of tDCS. For example, Merzagora et al. measured the

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HbO changes in resting state in the prefrontal cortex before and after tDCS;[16] in two other studies, researchers measured the sensorimotor cortex before, during, and after tDCS.[14,17] Although intuitive and effective, their methods are not appropriate for estimating the network properties of the cortex from fNIRS data. In this study, we investigated a functional brain connectivity measure, the coherence between fNIRS signals from two brain locations, to describe the underlying brain changes from fNIRS data.

Coherence is a well-known tool for measuring functional brain connectivity. It has been widely used to identify transient changes in the functional coupling of distributed neuronal assemblies via electroencephalography and magnetoencephalographic recordings.[18–24] However, its application to fNIRS has been rare. Homae et al. used fNIRS to investigate the development of global cortical networks in early infancy.[25] Inspired by this, in this study, we sought to investigate whether the coherence analysis of fNIRS data is able to measure the effects of tDCS on brain connectivity. We use the minimum variance distortionless response magnitude squared coherence (MVDR-MSC) method to calculate the coherence between fNIRS signals. The MVDR is a high resolution spectrum estimation method based on minimum variance and is effective at measuring coherence.[26,27]

To evaluate the effect of tDCS on fNIRS activities, anodal tDCS was applied to the left motor-related area of five healthy adults at rest. The fNIRS signals during two sessions were recorded and analyzed. The coherence of fNIRS signals was calculated and compared between the pre-tDCS, tDCS, and post-tDCS time segments to find out whether the cortical networks are influenced by tDCS.

The paper is organized as follows. First, we present the details of the subjects, fNIRS-tDCS setup, experiment protocol, and methods for evaluating the effects of tDCS. Second, we give the main results for the different stimulation phases. Finally, we discuss the potential explanations for our findings, as well as the advantages and disadvantages of the fNIRS-based coherence method.

2 Materials and Methods

2.1 *Subject Data*

In this study, we recruited five healthy university volunteers (2 females and 3 males, aged 19–25 years, mean ± SD 21.6 ± 2.4) to investigate the effects of anodal tDCS using fNIRS. All subjects were right handed as assessed by the Edinburgh Handedness Inventory scale.[28] Potential participants were excluded if they had a history of seizure, paroxysm, or hormonal, metabolic, circulatory, psychiatric or neurological illness, or were currently pregnant. Subjects were medication-free at the time of study. All subjects voluntarily provided informed consent at the beginning of the experiment. This study was approved by the ethics committee of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University. Information of all participants is summarized in Table 1.

Table 1 Information of the subjects.

Subject No.	Sex	Age	Education
1	Male	25	Graduate
2	Female	19	Undergraduate
3	Male	20	Undergraduate
4	Female	21	Undergraduate
5	Male	23	Undergraduate
	Total: 2F/3M	21.6 ± 2.4 (mean ± std)	

2.2 *Functional Near-Infrared Spectroscopy-Transcranial Direct Current Stimulation Setup*

The fNIRS-tDCS setup is shown in Fig. 1. A continuous wave optical topography system (ETG-4000, Hitachi Medical Company, Japan) was used to measure relative changes of oxy-hemoglobin (HbO) and deoxy-hemoglobin (Hb) signals induced by motor-related cortex activity before, during and after bi-hemispheric tDCS. tDCS was applied to the scalp using a battery-driven electrical stimulator (Neuro Conn DC-Stimulator, Germany) through a pair of sponge-covered rubber electrodes (7 cm × 5 cm in size, 35 cm^2) soaked in saline solution. The anodal electrode was centered over the left motor-related cortex and the cathode was positioned on the right dorsolateral supraorbital area. For fNIRS recording, we used one set of 3 × 2 measurement patches, one placed over the right parietal cortex. Note that the fNIRS recordings were made from contralateral cortex. Findings from previous studies, as noted in the discussion, give justification for this setup. A swimming cap was used to hold the probes against the scalp. Probes were plugged into the red or blue holes on the patches.

The absorption of near-infrared light at wavelengths 695 and 830 nm was measured with a sampling rate of 10 Hz. The fNIRS source detectors were positioned on the right motor-related area. Three detectors were distributed as in Fig. 1(b). Since fNIRS measures the HbO changes between emitters and detectors,

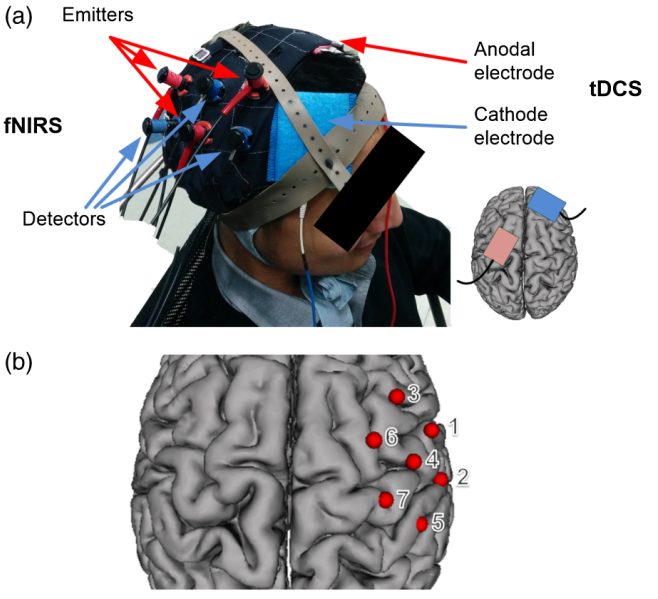

Fig. 1 The functional near-infrared spectroscopy (fNIRS) and transcranial direct current stimulation (tDCS) setup. (a) Photo of a subject wearing fNIRS and tDCS electrodes. The small plot at bottom right shows the tDCS electrodes mapped on the cortex. (b) Distribution of seven fNIRS channels, mapped on the cortex.

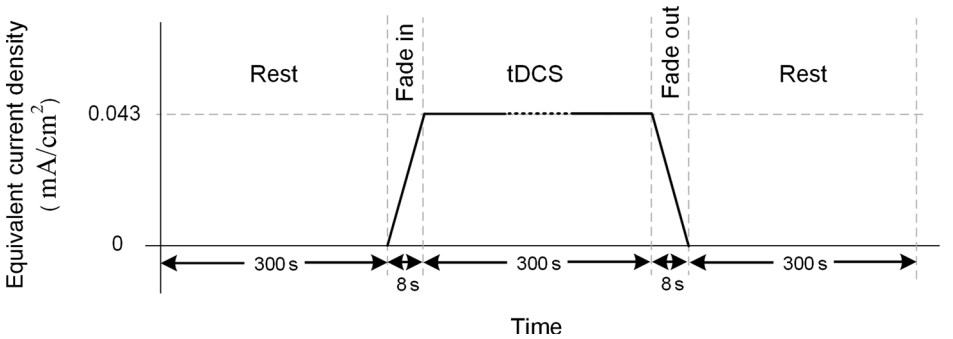

Fig. 2 The experimental protocol.

the actual number of fNIRS channels was 7, and the channels were distributed as in Fig. 1(b), mapped on a standard brain model.

2.3 *Experimental Protocol*

Each subject was instructed to be comfortably seated at a distance of 80 cm from a 19-inch monitor in a quiet room and to avoid movements. They were also asked to fix gaze on a white cross on the black screen without falling asleep during the entire session. The anodal tDCS was delivered with a current of 1.5 mA (equivalent current density: 0.043 mA/cm^2) for 5 min. The single-mode stimulation was applied with 8 s of fade in and fade out, with a total stimulation time of 316 s. The cortical activity in the regions of interest was measured by fNIRS before, during, and after applying anodal tDCS. We first collected baseline fNIRS signals for 5 min during the rest state before tDCS. Then, fNIRS signals were recorded continuously for 5 min during tDCS and for 5 min after stimulation terminated. The whole protocol can be found in Fig. 2.

3 Methods

The MVDR-MSC method was used to calculate the coherence between fNIRS signals and to obtain the correlation matrix. Then the global synchronization index of the correlation matrix was calculated using the S-estimator method.

3.1 *Minimum Variance Distortion-Less Response Magnitude Squared Coherence Algorithm*

The MVDR spectrum estimation method[29] models spectra by using linear prediction.[30] MVDR-MSC is better than Welch-MSC in frequency sensitivity and precision.[29] An m'th order MVDR spectrum is computed by

$$S(f) = \frac{1}{|\sum_{k=-m}^{m} \mu(k) e^{-j2\pi fk}|^2},$$

where f is the frequency, m is the MVDR filter order, k is an iterator whose values determine the frequency resolution, and the parameters $\mu(k)$ are computed by a simple noniterative method from the linear prediction coefficients.[29]

We define the magnitude squared coherence (MSC) function between two fNIRS signals $x_1(n)$ and $x_2(n)$ as

$$\gamma^2_{x_1x_2}(f) = \frac{|E(S_{x_1}(f)S^*_{x_2}(f))|^2}{E|S_{x_1}(f)|^2 E|S_{x_2}(f)|^2}, \quad (2)$$

where * denotes the conjugate of a complex number and $E(X)$ is the expectation of the windowed X.

For fNIRS data with L channels, we obtain the correlation matrix using the output of the MVDR-MSC algorithm. We denote the matrix as C, and its element at the i'th row, j'th column is $\gamma_{x_ix_j}$. The correlation matrix is symmetric, and when $i = j$, $\gamma_{x_ix_j} = 1$. Since MVDR-MSC calculates the phase correlation, the correlation matrix C describes the phase relationship between channels.

3.2 *Global Synchronization Index*

In this study, we use the global synchronization index (GSI) to assess synchronization in multivariate neural data signals by examining the distributions of the eigenvalues of the correlation matrix $\mathbf{C}$.[31] The eigenvalue decomposition of $\mathbf{C}$ is

$$\mathbf{C}\mathbf{v}_i = \lambda_i \mathbf{v}_i, \quad (3)$$

where eigenvalues $\lambda_1 \leq \ldots \leq \lambda_l \leq \ldots \leq \lambda_L$ are in increasing order, and $\mathbf{v}_i$, $i = 1, \ldots, L$ are the corresponding eigenvectors. As C is a real symmetric matrix, all eigenvalues are real numbers, and the trace of C is equal to the number of channels L. When all the channels perfectly correlate, the entries of matrix C are all equal to 1, the maximum eigenvalue is L and the others are zeroes.

The normalized eigenvalues $\bar{\lambda}_l$ of the fNIRS correlation matrix are as follows:

$$\bar{\lambda}_l = \frac{\lambda_l}{\sum_{i=1}^{L} \lambda_i}, \quad l = 1,2, \cdots, L. \quad (4)$$

The GSI is defined as follows:

$$\mathrm{GSI} = 1 + \frac{\sum_{i=1}^{L} \bar{\lambda}_l \log(\bar{\lambda}_l)}{\log(L)}. \quad (5)$$

The GSI is a measure of the total amount of synchronization.[31] After calculating the GSI, we used the t test to test for statistically significant differences between the pre-tDCS, tDCS, and post-tDCS time stages.

4 Results

The effect of tDCS on the HbO was first investigated. We analyzed the HbO changes pre, during, and post-tDCS. The analyzed frequencies ranged from 0.04 to 0.15 Hz, similar to previous low-frequency fluctuation studies of fNIRS signals.[32–34] For each stage, the absolute energy changes were averaged

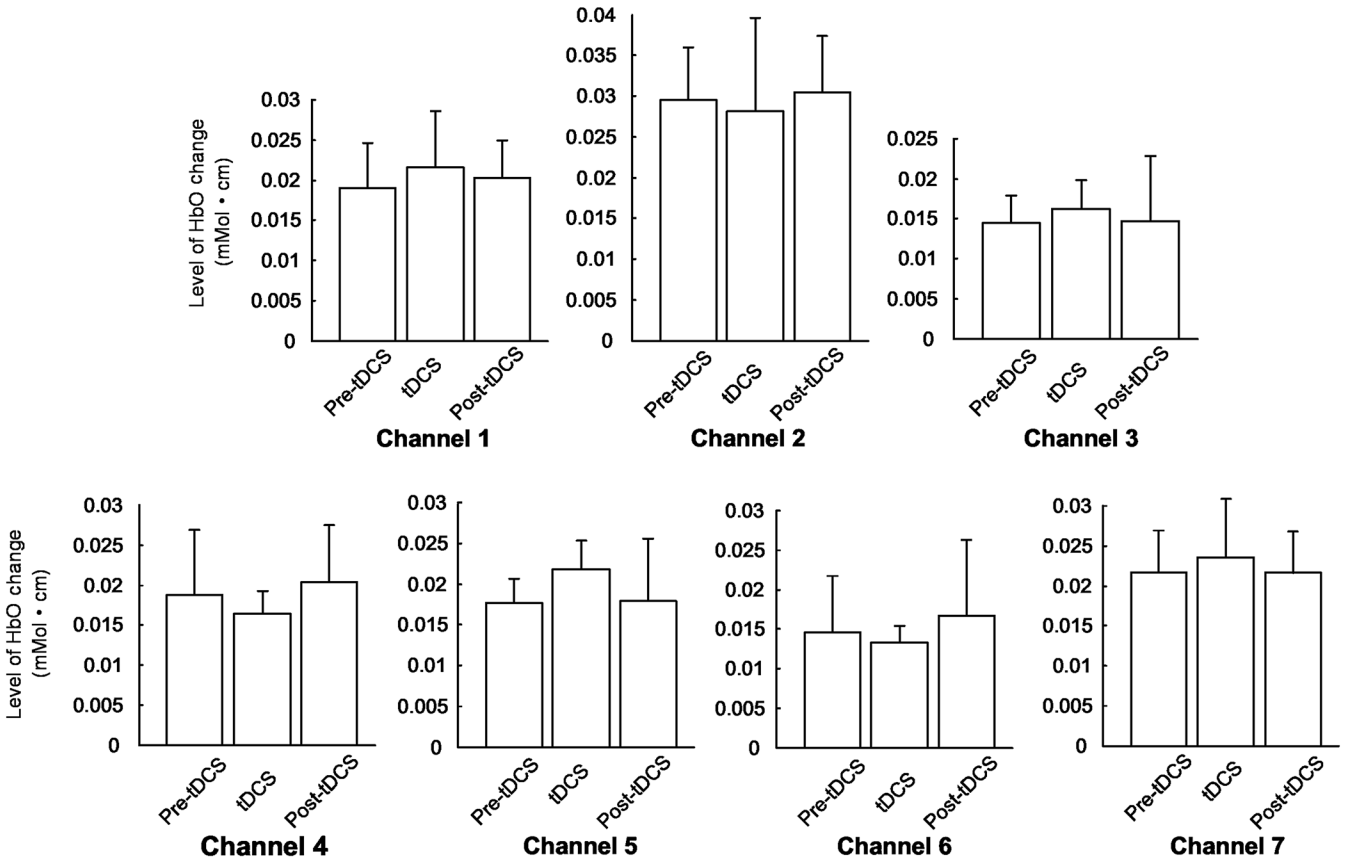

Fig. 3 The statistics of HbO changes in pre-tDCS, tDCS, and post-tDCS stages for each channel.

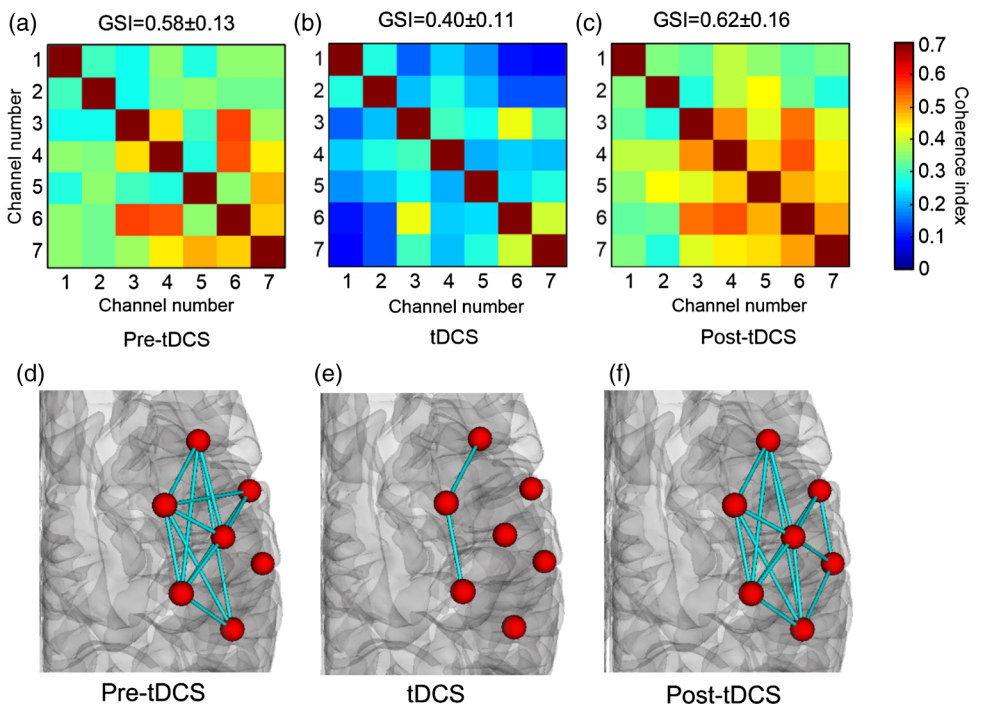

Fig. 4 The mean coherence matrices of fNIRS signals for five subjects during the three experiment stages and their visualization as network connectivity strengths: (a–c) coherence matrix for pre-tDCS, tDCS, and post-tDCS, respectively. The color of tiles (see color bar) indicates the strength of coherence between two channels. Corresponding global synchronization index (GSI) values are marked above the plots. (d–f) The binarized functional networks for (a–c), respectively. The color of each edge represents the coherence strength between two nodes. The binarization used the median of coherence values as the threshold.

for every channel across all subjects. The difference in energy change between stages for each channel was tested using a two-sample t test. As shown in Fig. 3, we can see that the HbO change level increased for some channels, and decreased for others, but all differences between the three stages were not statistically significant.

The effect of tDCS on the phase relationship between the HbO series was then investigated. We measured the phase relationship between fNIRS signals by calculating the coherence using MVDR between each pair of channels of the HbO data. The all-subject-mean coherence matrices of the seven fNIRS signals for each time stage are shown in Figs. 4(a)–4(c). The tiles along the diagonal line of each matrix indicate self-coherence, which is equal to 1. As can be seen from Figs. 4(a)–4(c), there was a significant difference in coherence between fNIRS signals at the pre- and post-tDCS.

To provide an intuitive summary of the differences in coherence between time stages, we computed the GSI from each of the coherence matrices. The GSIs for the coherence matrices of pre-tDCS, tDCS, and post-tDCS for all subjects are plotted at the top of Figs. 4(a)–4(c). We found statistically significant differences in GSIs between pre-tDCS and tDCS time stages ($p < 0.05$, $N = 5$, t test) and between tDCS and post-tDCS time stages ($p < 0.05$, $N = 5$, t test). However, the difference in GSI between pre-tDCS and post-tDCS time stages was not statistically significant ($p > 0.05$, $N = 5$, t test). These findings indicate a decrease in intraregional synchronization induced by tDCS.

To better reveal the changes in functional connectivity, we converted the coherence matrices into a binary network using a threshold, which is determined by the median of coherence values. The resulting networks are shown in Figs. 4(d)–4(f). During tDCS, the functional connection between fNIRS signals decreased. After stimulation, the connection strength increased. This suggests that tDCS has a strong impact on brain functional connectivity, as measured by hemodynamic changes, and that the coherence matrix is capable of evaluating the effects of tDCS.

5 Discussion and Conclusion

In this study, we investigated the online effect of 1.5 mA tDCS applied to the left motor-related cortex to fNIRS signals obtained from the contralateral right motor-related cortex at the pre-tDCS, tDCS, and post-tDCS time stages. We found that (1) the level of HbO change at the right motor-related cortex area showed no significant difference during tDCS; (2) the coherence between certain channels at the right motor-related cortex area decreased during tDCS; and (3) the contralateral functional brain connectivity (GSI) calculated by MVDR-MSC decreased significantly during tDCS. These results suggest an interesting relationship between the effects of tDCS and metabolic signals of contralateral motor-related cortex.

In a previous study,[35] researchers have demonstrated that the tDCS over the left motor area can influence contralateral and ipsilateral finger sequence movements. Another study also demonstrated that rTMS over the left motor hand area can decrease interhemispherical inhibition from the left-to-right hemisphere and increase the amplitude of motor evoked potentials evoked from the right hemisphere.[36] Our findings are congruent with previous studies and support the hypothesis that tDCS can influence the contralateral brain area.

In this study, we explored the responses in hemodynamics to tDCS in healthy individuals by estimating the functional connectivity within the contralateral motor-related cortex and determined that the tDCS can result in a decrease in functional connectivity within the contralateral motor-related cortex. In a similar study,[12] researchers have demonstrated, by fMRI, that unilateral anode tDCS over the right motor-related cortex (cathode over the contralateral supraorbital region) caused a decrease in intracortical functional connectivity within the right motor-related area during stimulation. This is consistent with our findings as well.

Despite efforts made in recent decades to characterize and better understand the effects induced by tDCS,[37] the underlying neurophysiological mechanisms have not yet been clearly revealed. Previous pharmacological studies suggest that the cortical excitability changes produced by anodal tDCS are GABAA and NMDA receptor-dependent.[38–40] We propose that a possible explanation of the observed decrease of coherence during tDCS is that unilateral tDCS can increase excitability in the left motor-related area, and this excitability can be transferred to the right motor-related area via cross-hemispheric connections, which in turn influences the hemodynamics. A previous study has also found a bilateral increase in cerebral excitability during and after tDCS.[41] The decrease in functional connectivity was presumably caused by a decrease in synchrony of low frequency fluctuations which in turn resulted in a functional decoupling between motor cortex areas. [12] However, the exact neurophysiological mechanism underlying the phenomenon remains an open question.

FNIRS, particularly when combined with functional connectivity analysis, may be a useful tool for describing the effects of tDCS. First and foremost, fNIRS, an optical technology, is not susceptible to interference from tDCS. FNIRS provides information about the spatial-temporal trends in tDCS effects. Coherence-based analysis may reveal the effects of tDCS on resting-state functional connectivity, which may be indicative of neuroplasticity.

Based on these advantages, we suggest that fNIRS can be used for describing the online and after-effects of tDCS, designing appropriate stimulation protocols, and finding optimal stimulation parameters (such as current duration and strength) for clinical rehabilitation. The current study is limited in sample size and measurement duration; future studies should use fNIRS to investigate the long-term effects of tDCS on a larger number of subjects, as well as whether the induced changes in functional connectivity correlate with performance on various tasks.

However, fNIRS-based connectivity analysis has limitations. One limitation is its low temporal resolution, as fNIRS observes the relatively slow metabolic correlations of brain activity. This makes fNIRS-based analysis unsuitable for paradigms requiring fast responses. Also, the information flow between different brain areas is difficult to obtain because the information's frequency content is typically far higher than fNIRS's temporal resolution. Limitations also include its restricted spatial coverage (shallow cortical areas only) and modest number of recording channels.

In conclusion, we combined fNIRS recordings with coherence-based functional connectivity analysis to investigate the changes in brain activity induced by tDCS during a rest state. The results showed a possible relationship between electrical stimulation and brain activity change in terms of hemodynamic changes. The fNIRS-based multichannel analysis used here is a promising tool for future studies on tDCS.

Acknowledgments

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