Neuromodulatory Effects of HD-tACS/tDCS on the Prefrontal Cortex: A Resting-State fNIRS-EEG Study

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***Abstract*—Transcranial direct and alternating current stimulation (tDCS and tACS, respectively) can modulate human brain dynamics and cognition. However, these modalities have not been compared using multiple imaging techniques concurrently. In this study, 15 participants participated in an experiment involving two sessions with a gap of 10 days. In the first and second sessions, tACS and tDCS were administered to the participants. The anode for tDCS was positioned at point FpZ, and four cathodes were positioned over the left and right prefrontal cortices (PFCs) to target the frontal regions simultaneously. tDCS was administered with 1 mA current. tACS was supplied with a current of 1 mA (zero-to-peak value) at 10 Hz frequency. Stimulation was applied concomitantly with functional near-infrared spectroscopy and electroencephalography acquisitions in the resting-state. The statistical test showed significant alteration ($p < 0.001$) in the mean hemodynamic responses during and after tDCS and tACS periods. Between-group comparison revealed a significantly less ($p < 0.001$) change in the mean hemodynamic response caused by tACS compared with tDCS. As hypothesized, we successfully increased the hemodynamics in both left and right PFCs using tDCS and tACS. Moreover, a significant increase in alpha-band power ($p < 0.01$) and low beta band power ($p < 0.05$) due to tACS was observed after the stimulation period. Although tDCS is not frequency-specific, it increased but not significantly ($p > 0.05$) the powers of most bands including delta, theta, alpha, low beta, high beta, and gamma. These findings suggest that both hemispheres can be targeted and that both tACS and tDCS are equally effective in high-definition configurations, which may be of clinical relevance.**

***Index Terms*—Electroencephalogram (EEG), functional near-infrared spectroscopy (fNIRS), prefrontal cortex (PFC), hemodynamic response (HR), transcranial alternating current stimulation (tACS), transcranial direct current stimulation (tDCS), cognition.**

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I. Introduction

TRANSCRANIAL electric stimulation (tES) is a noninvasive technique that includes transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation. These stimulation techniques are widely applied in clinical and cognitive sciences [1]. To modulate brain excitability, either low-intensity (typically 0.5–2 mA) DC or AC is applied over the scalp using surface electrodes. It is assumed that tDCS alters neuronal activity by pushing the resting membrane potential toward either depolarization or hyperpolarization depending upon the stimulation type [2]. One type of tDCS is anodal stimulation, which is assumed to increase neuronal firing under a particular stimulation electrode. This stimulation results in improved task performance [3]–[5]. In contrast, cathodal stimulation suppresses neuronal firing, resulting in low task performance [6]–[12]. Meanwhile, neural oscillations in the brain during mental activities can be modulated by tACS [13], [14]. Several studies have reported abnormalities in such oscillations in patients with neuropsychiatric disorders, and these abnormalities may underpin their pathophysiology [14], [15]. Therefore, tACS application enables interaction with brain oscillations, thereby allowing the latter to be modified via 0.5-2 mA level electric current regulated to the rhythms of endogenous oscillations through the scalp [16]–[19]. This noninvasive neuromodulation technology is promising for therapeutic interventions in oscillopathies [20].

The combination of tES with measurement through functional imaging techniques may provide promising outcomes for studying neuromodulatory effects. Researchers reported that tES could alter hemodynamic responses by modulating cortical neurotransmitters and enhancing neuronal activity via an induced electric field [21], [22]. Furthermore, it is evident that cerebral blood flow is modulated by tDCS and transcranial infrared laser stimulation [23]. Among functional neuroimaging modalities, functional near-infrared spectroscopy (fNIRS) is a portable, noninvasive, and clinically available tool. fNIRS measures changes in the hemodynamic response (changes in the concentration of oxygenated and deoxygenated hemoglobin), providing good spatial and temporal resolution. Furthermore, its combination with other modalities such as electroencephalography (EEG) may provide more insights into the brain with a significantly better temporal resolution.

However, EEG results can support fNIRS findings before and after the stimulation period, not during the stimulation period. Because concurrent tES can influence EEG acquisition while the optical signals of fNIRS are unaffected by electrical inputs. Many studies have been conducted to evaluate the effects of tDCS on hemodynamics during or after working memory tasks [24]–[30]. A montage with multiple cathodes arranged in a ring/square around an anode as the center or at a particular place is known as a high-definition (HD) montage, which is useful for containing an electrical field to a targeted brain area [31]–[35]. Compared with stimulation's conventional and focal effects, HD-tDCS-generated neuroplasticity remains for longer periods [36]. Merzagora *et al.* [37] evaluated cortical changes in the prefrontal cortex (PFC) of healthy subjects using fNIRS during the resting-state. Working memory ability differentially affects responses to tDCS and HD-tDCS in retro-cue tasks [38]. Muthalib *et al.* [39] observed a significant increase in oxyhemoglobin concentration in the sensorimotor cortex where HD-tDCS was administered, whereas minimal effects were observed in the contralateral non-stimulated region [39]. Yaqub *et al.* [40] applied an HD-tDCS montage to one hemisphere of the PFC and systematically compared intrahemispheric and interhemispheric connectivity changes. In a stroke patient study [41], joint imaging with fNIRS and EEG was used to assess the neurovascular coupling during tDCS. Sood *et al.* [42] extended the study of Datta *et al.* [41] by providing a parameter estimation method to obtain a relationship between EEG band power and the changes in fNIRS oxyhemoglobin signals during tDCS. In [43], the improvement of neuronal activity and learning using tDCS for pilot training was reported. Hemodynamic and power changes were observed due to stimulation in a feasibility study of time-resolved fNIRS and EEG [44]. Recently, several computational, experimental, and methodological studies were conducted in conjunction with joint imaging for assessing the best outcomes of tDCS in healthy participants or patients [46]–[50]. The results are convincing from the tDCS and fNIRS/EEG studies, but there is heterogeneity in the reported results. It may be due to the different analysis approaches and differences in measurement acquisitions and factors that may interfere with tDCS outcomes, such as current intensity, stimulation time, electrode sizes, and montage [51]–[53]. Also, the extension of computational modeling-based studies to large cohorts is still lacking.

In clinical and cognitive studies, the PFC of the brain is often targeted for tES. Dorsolateral PFCs have been modulated to improve cognitive functions such as memory, attention, and multitasking and treat various psychiatric disorders, such as major depressive disorders and autism [54]–[58]. Researchers have extensively investigated the after-effects of tACS on working memory capacity, perception, multitasking, motor control, and learning [59]–[67]. Some additional and critical physiological analyses relied primarily on the resting-state measurements after tACS [61]. Zaehle *et al.* [68] observed a power increase at the individual alpha frequency after tACS. An elevated power at the individual alpha frequency after 20 min tACS, lasting for 70 min, was observed in another study [69], indicating that alpha tACS can increase the amplitude of the alpha frequency. In most of these studies, tES was administered during the resting state by placing anode and cathode electrodes on the dorsolateral PFCs (i.e., anode at F3 and cathode at F4 as per the International 10–20 System). In the combined fNIRS and EEG study [70], an elevated power but no significant change in the hemodynamic responses after tACS were reported. Many studies have demonstrated tES-induced brain connectivity changes delivered to either the targeted primary motor cortex or only a hemisphere of the PFC (see [71], a review paper). The authors of [71] pointed out that tES could change the resting-state functional connectivity of the channels within the stimulated area and further between the stimulated area and distal locations away from the stimulated area. Also, in a paper targeting a single dorsolateral PFC, tDCS could modulate the functional connectivity of the frontoparietal networks involved in cognitive functions [72]. However, the effects of tES montages targeting both hemispheres of the PFC, in terms of hemodynamics and the EEG band powers, are yet to be fully elucidated.

Nevertheless, the exact mechanism of tES-induced after-effects remains controversial because of different stimulation parameters across studies, including duration, frequency, intensity, and electrode montage, as well as incomplete knowledge regarding the underlying neurophysiological mechanisms. In addition, the correctness of EEG measurements is susceptible during tES due to electrical artifacts. Furthermore, hemodynamic changes during stimulation are not fully understood, specifically during tACS. Likewise, the effects of HD-tACS/tDCS applied over the PFC in the resting-state are yet to be investigated using fNIRS and EEG simultaneously. Hence, hybrid fNIRS–EEG can be combined with either tDCS or tACS with no electro-optic intervention to measure the hemodynamic response during electrical stimulation.

This study comprehensively compares the effects of tDCS and tACS on the PFC using fNIRS and EEG. Another aspect is to check the placement of high-definition montage so that both hemispheres of the PFC can be targeted simultaneously. We hypothesized that tDCS and tACS would cause PFC activation during resting-state measurement. It is largely unknown that the oscillatory type of current, as in tACS, would cause any changes to hemodynamics or not. Although, the enhancement of an alpha-band frequency could be expected to match the driving frequency with intrinsic brain oscillations. Further, we sought to determine what changes would occur in the EEG band-wise powers when tDCS and tACS (at 10 Hz) were administered. We argue that combining EEG and fNIRS to analyze tACS and tDCS is essential for understanding the effects and clinical implementation. Through that, we can achieve a multidimensional perspective on basic neural mechanisms. In summary, we analyzed the hemodynamic changes before, during, and after tDCS and tACS were applied. The EEG band powers were analyzed before and after the stimulations, not during the stimulation. The knowledge of tACS/tDCS effects on both hemispheres will help develop clinical procedures for treating patients with mental disorders.

II. Materials and Methods

A. Subjects

We performed a pilot experiment of twelve-minute tDCS with two subjects. Using the mean (i.e., 3.687e-04) and standard deviation (i.e., 5.433e-04) from the pilot experiment, we computed the needed subject number using the method provided on the website [73]. The used statistical criteria were a two-sided test with a 5% significance level, with the statistical power to be 80%. The computed sample size was fifteen. A total of eighteen subjects were recruited.

In tACS experiments, two subjects had a problem: One felt severe phosphene, and another subject's forehead was too hairy. In the case of tDCS experiments, one subject's fNIRS data were corrupted. As a result, three subjects were excluded in the final analysis stage. The mean age and standard deviation of the fifteen subjects were 29 and 3.2, respectively. All participants were graduate students at Pusan National University and had a normal or corrected-to-normal vision. None of them had a history of neurological or psychiatric problems. None used neuroleptic, hypnotic, or antiseizure medications. Since only male subjects were recruited, the sample group was homogeneous. The participants were allowed to quit if they encountered any difficulty during the experiment. Some subjects had experience in brain signal acquisition experiments, whereas only two participants had tDCS experience. Prior to the start of the experiment, all the participants were informed about the study procedure and associated risks. The participants provided written informed consent upon agreeing with the terms. All procedures in this study were done in accordance with the latest Declaration of Helsinki, approved by the local ethics committee of Pusan National University.

B. Neuroimaging Acquisition and Preprocessing

In this study, a g.Nautilus fNIRS-8 (g-tec medical engineering GmbH, Austria) portable multimodal device with wireless technology that allows combined recordings of EEG and fNIRS signals was used. Both EEG and fNIRS signals were recorded synchronously using the MATLAB-Simulink platform at a sampling rate of 250 Hz. The system used two wavelengths (760 and 850 nm) of near-infrared light to obtain raw fNIRS data. The brain signals were wirelessly transmitted to a laptop, where the optical intensity, their conversion to concentration changes of oxygenated and deoxygenated hemoglobin (ΔHbO/ΔHbR) using the modified Beer–Lambert law, and EEG signals were displayed in real-time and saved in a MATLAB workspace at the end of experiments. For offline analysis, the obtained resting-state fNIRS signals were passed through a fourth-order Butterworth low-pass filter with a cut-off frequency of 0.1 Hz [39]. For the EEG analysis, results obtained before and after the stimulation period were considered. All EEG and fNIRS data were analyzed offline using MATLAB^{TM} 17.0 (MathWorks, USA) software. The EEG data were bandpass-filtered (fourth-order) using MATLAB function *filfilt* in the frequency range of 1–50 Hz. The power spectral density (PSD)/power spectrum was calculated for individual channels/subjects using MATLAB function *pwelch* with a hamming window size of 500 (data points) while the half-length of window size for the overlap was 250 (data points). The EEG-band powers for each channel/subject were analyzed by the wavelet transform (Morlet wavelet) with 0.5 frequency step. Thirty epochs of 2 sec each were chosen in before and after the stimulation periods. Outliers were removed considering two sigmas and mean power of all epochs were calculated. In this work, the calculated EEG bands were the delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), low beta (12–18 Hz), high beta (18–30 Hz), and gamma (30–50 Hz) bands.

In this paper, another index was introduced, i.e., the band-wise power distribution. It is the distribution of the total power in the considered bands. In this paper, the powers in the delta, theta, alpha, low beta, high beta, and gamma bands were individually computed and divided by the total power of the frequency range 1$\sim$50 Hz, showing the percentage distribution of the total power into the bands.

C. Channel Configuration

The placement of the EEG electrodes and fNIRS optodes is shown in Fig. 1. In the present study, two detectors and eight sources (see Fig. 1) were used to form eight fNIRS channels to investigate the PFC of the human brain. In accordance with the International 10–20 System of EEG electrode placement, the sources were positioned on the PFC by considering FpZ as the reference point. Eight channels were configured using source–detector combinations. The g.Nautilus fNIRS-8 headset was used for the placement of EEG electrodes and fNIRS optodes. All the sources and detectors were placed approximately 3 cm apart. The source-detector pairs exceeding 5 cm distance might result in noisy and unreliable signals [74]. In addition, six EEG electrodes were used to acquire electrical potential changes on the surface of the forehead concurrently.

D. HD-tACS/tDCS

Electrical stimulation was provided by a battery-driven Starstim tES system (Neuroelectrics, Barcelona, Spain). The tES system comprises eight electrodes, of which five electrodes (four cathodes, one anode) were used in 4×1 HD-tDCS and HD-tACS electrode configurations. Each electrode was made of AgCl and had a diameter of 1 cm. The middle electrode was anode, whereas the remaining four were return electrodes (cathodes) attached to the skin with conduction-enhancing gel-filled foam (Kendall^{TM} Conductive Adhesive Hydrogel; Medtronic, Minneapolis, MN, USA). The gel-filled foams were used only once per subject. The HD configuration of electrodes was placed on the PFC such that the anode was positioned approximately 4 and 6 cm away from the returning electrodes, as indicated in Fig. 1. The current capacity of tDCS through the anode was set to 1 mA. tACS provided 1 mA amplitude (i.e., the zero-to-peak) at 10 Hz belonging to the alpha band. The stimulation parameters were selected based on the existing literature [58], [65], [71]. The tES system was connected to a computer through Bluetooth, and electrodes were configured using the Bluetooth software (Neuroelectrics Instrument Controller 2.0; Neuroelectrics). In

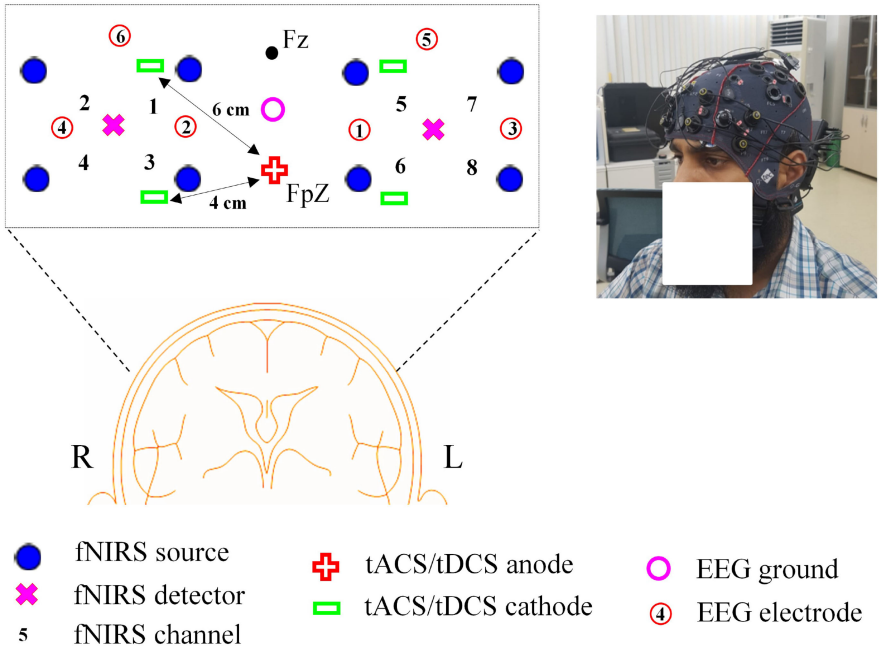

Fig. 1. Concurrent arrangement of fNIRS and EEG electrodes along with HD-tDCS/tACS electrodes.

this study, the stimulation protocol was programmed using the software, including the electrode placement (i.e., one anode and four return electrodes) and the current distribution (i.e., 25% per return electrode).

E. Experimental Paradigm

The experimental paradigm consists of three phases: a 6-min pre-stimulation duration, followed by a 12-min stimulation period, and a 12-min post-stimulation period. Preparation of tES electrodes and fNIRS optodes took approximately 25 min. After the setup, the total experiment lasted for 30 min. A 12-min stimulation (tDCS or tACS) including 15-s ramp-up and 15-s ramp-down at the beginning and the end of the stimulation period, respectively, was performed. Initial 1-min data is excluded in the fNIRS analysis as many subjects moved a bit in this period to settle down. During the experiment, all participants were asked to sit comfortably in a chair and keep their eyes closed. They were instructed not to sleep during the experiment. The positions of the stimulation electrodes were first marked on the PFC of the participants after they wore the g.Nautilus fNIRS-8 headset. Subsequently, the headset was removed. The adhesive electrodes were placed in the marked places. Next, the headset was worn again such that the top of the electrodes protruded from the holes. Subsequently, the fNIRS probes and EEG electrodes were placed at the measurement sites. The gel was filled in the EEG electrodes for better signal transmissions.

F. Questionnaire on Adverse Effects

All participants were asked to assess the possible side effects of the stimulation by completing a questionnaire [57]. They were instructed to rate the intensity on a scale of 1 (low), 2 (medium), and 3 (high) for the following side effects: tingling, fatigue, itching, pain, burning sensation, phosphene, and bumping.

G. Statistical Analysis

The Wilcoxon matched-pairs signed-rank test (shortly Wilcoxon test) was used when comparing two data sets not conforming to the normality condition. However, a paired *t*-test was used for those data sets conforming to the normality. In this paper, the Wilcoxon test was carried out for comparing fNIRS data sets from tACS/tDCS (i.e., fNIRS channel-wise comparison, tACS effect vs. tDCS effect, nearby fNIRS channel vs. distal fNIRS channel, etc.). On the other hand, when analyzing the mean EEG band powers before and after stimulation, a paired *t*-test was utilized. Also, the Wilcoxon test was applied to check the questionnaire-based effects of tDCS and tACS. In all statistical analyses, a *p*-value of less than 0.05 was considered significant.

III. Results

A. Safety and Tolerability of tES/fNIRS/EEG

In both stimulation cases (tDCS, tACS), no severe adverse effects were observed. In between-stimulation condition comparisons, no difference was observed for any side effect, except for fatigue and tingling. Statistically, tingling was greater in tACS than in tDCS ($p < 0.05$). Also, fatigue was greater in the tACS group than in the tDCS group ($p < 0.05$). Additionally, almost all the participants in the tACS group reported medium to severe phosphene and bumping effects. This effect may be due to the proximity of the stimulation/return electrodes in the PFC near the eyes. In contrast, no phosphene effect was reported by the participants in the tDCS group.

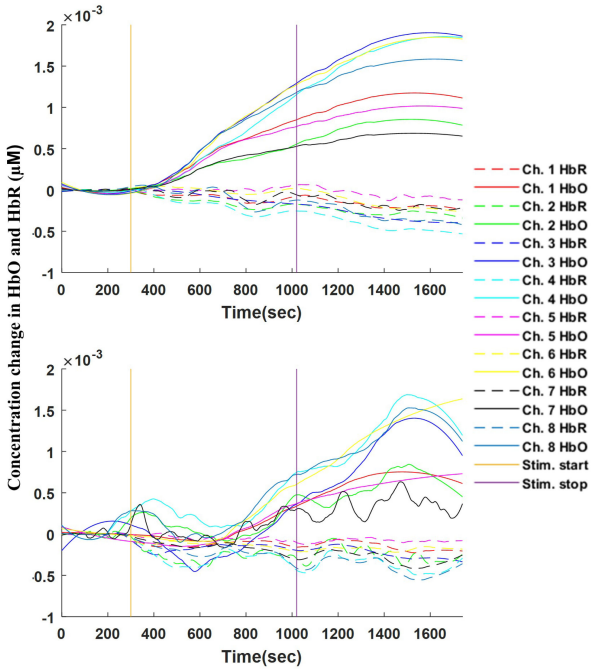

Fig. 2. Mean hemodynamic responses of all subjects obtained by HD-tDCS (upper panel) and HD-tACS (lower panel). "Ch." and "Stim." are abbreviations for "channels" and "stimulation," respectively. The hemodynamic responses significantly increased upon stimulation and kept the maximum level throughout the entire poststimulation period.

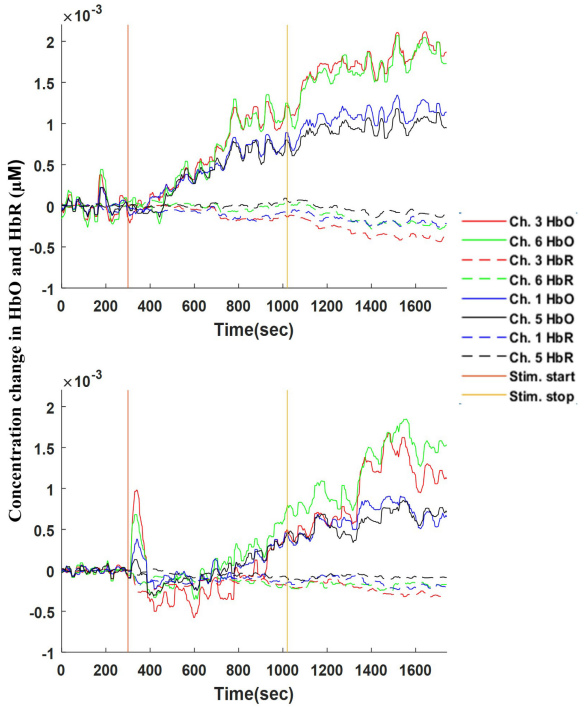

Fig. 3. Mean ΔHbO/ΔHbR comparison of the channels located 4 cm apart (i.e., channels 3 and 6) and 6 cm apart (i.e., channels 1 and 5) from the anode: HD-tDCS (upper panel) and HD-tACS (lower panel). A significant increase is shown in Ch. 3 (mean ΔHbO: 9.5304e-04) and Ch. 6 (mean ΔHbO: 9.2300e-04) with tDCS, (i.e., near the anode). On the contrary, a less increase is shown in Ch. 1 (6.2174e-04) and Ch. 5 (5.4852e-04) in the channels far from the anode. Similar behaviour is observed from tACS too: Ch. 1 (mean 2.8085e-04), Ch. 5 (2.4585e-04), Ch. 3 (3.6654e-04), and Ch. 6 (5.4919e-04).

B. Average Hemodynamic Changes in Resting-State Due to HD-tACS/tDCS

The effect of HD-tDCS/tACS on ΔHbO and ΔHbR was analyzed in three time windows: before, during, and after stimulation. Fig. 2 shows the mean ΔHbO and ΔHbR calculated from the averaged data of all subjects for all channels. Additional MATLAB smoothing function *sgolay* was applied to make the signal smooth for better representation. The ΔHbO and ΔHbR values increased and decreased significantly after the start of the stimulation phase ($p < 0.05$), respectively. The increase in responses sustained after the initial increase and continued through the stimulation phase on both the left and right sides of the PFC. ΔHbO stabilized at the maximum level when the stimulation window was completed, where it remained throughout the entire post-stimulation period. In tACS, the initial increase in ΔHbO was greater than that of tDCS, but the response decreased and then increased steadily subsequently. In contrast, the tDCS response increased gradually from the beginning of stimulation and stabilized after the stimulation phase. Additionally, ΔHbO increased more in some channels (i.e., channels 3 and 6) near the stimulation site (anode); however, in the channels far from the anode (i.e., channels 1 and 5) the increase was significantly less ($p < 0.05$). This behavior was observed in both stimulation cases, as shown in Fig. 3

C. Subject-Wise Hemodynamic Changes Due to HD-tACS/tDCS

Fig. 4 presents subjects showing an apparent increase in ΔHbO in both tDCS and tACS at the onset of stimulation. Although the hemodynamic changes did not appear coherently across all subjects, the average results were consistent and within subjects, as shown in Fig. 4. In Fig. 5, the average response of all subjects based on hemispheric division is depicted. It appeared that the ΔHbO responses of the left and right sides were similar; the mean response caused by tACS was lower than that by tDCS ($p < 0.05$). Similar behavior was observed in the ΔHbR case. Because the proportion of ΔHbR was less than that of ΔHbO, ΔHbR could not be viewed easily, as shown in Fig. 5. A similar trend in terms of a hemodynamic difference in tDCS/tACS can be observed by averaging the stimulated (right: channels 1 and 3; left: channels 5 and 6) and non-stimulated (right: channels 2 and 4; left: channel 7 and 8) channels hemisphere wise, as shown in Fig. 6.

D. Power Spectral Density Changes Due to HD-tACS/tDCS

The EEG analyses were performed before and after the stimulation period, as the supplied current during the stimulation period caused significant noise in the measured EEG signals. However, fNIRS is free from this issue as it is not subject to electro-optic interference.

In Fig. 7, the mean band powers of six bands are displayed: (a) tACS, (b) tDCS. Distributions of individual band powers

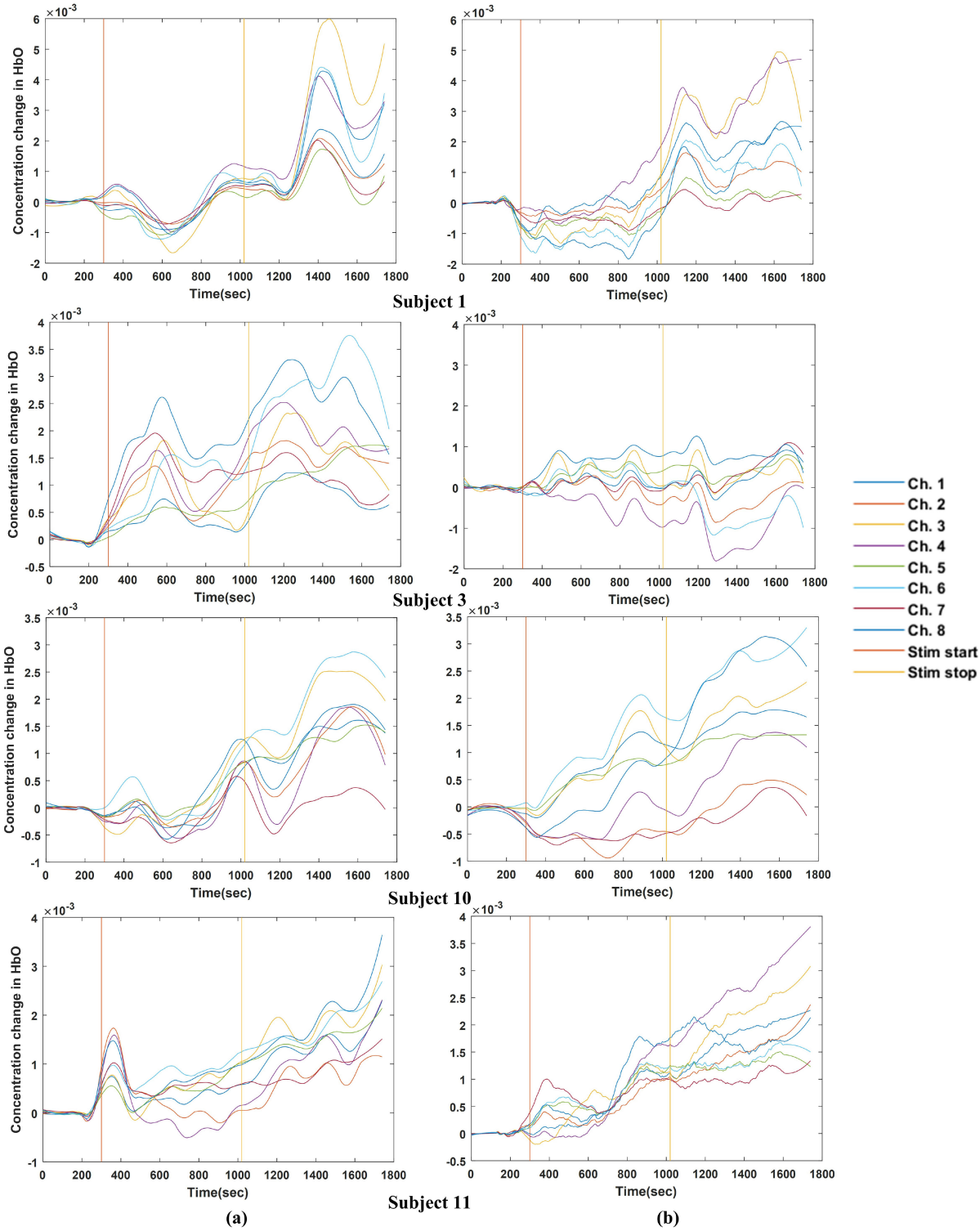

Fig. 4. All channel results of change in HbO of four participants subjected to (a) HD-tACS and (b) HD-tDCS. An increasing trend of hemodynamics can be seen in most of the subjects regardless of the stimulation type.

are well depicted. After HD-tACS, the powers of alpha ($p < 0.01$) and low beta ($p < 0.05$) increased significantly after the stimulation period. Although a decrease in the delta band was observed in Fig. 7(left panel), not significant ($p < 0.46$). However, such frequency-specific effects of tDCS was not seen. Although an overall improvement throughout the bands were observed. Statistically not significant increases in delta ($p = 0.13$), theta ($p = 0.09$), alpha ($p = 0.31$), low beta ($p = 0.09$), high beta ($p = 0.13$), and gamma ($p = 0.41$) were observed.

The PSD of all the EEG channels are shown in Fig. 8. In tACS, a visible increase in alpha power was observed in all channels after stimulation. The frequency spectra of all channels

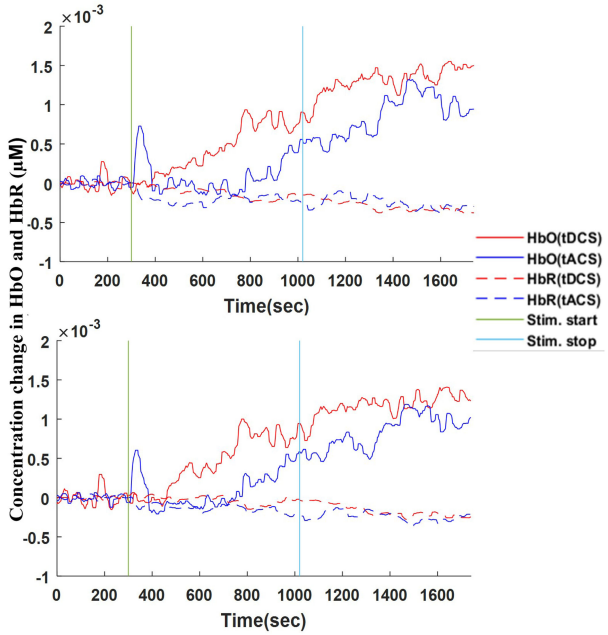

Fig. 5. Average ΔHbO/ΔHbR comparison of fNIRS channels located on the right (upper panel) and left (lower panel) PFC. A continual increase in HbOs is observed in both sides. In the right PFC, an increased mean ΔHbO caused by tDCS (7.2024e-4) is observed in comparison to tACS (i.e., 3.9052e-4). Similarly, a mean difference of ΔHbO 2.86e-4 is seen in the left PFC.

in tDCS indicate an small increase that illustrates the less impact in comparison to tACS.

The percentage band-wise power distribution in HD-tACS and HD-tDCS are shown in Fig. 9. After tACS, a significant decrease in delta (from 36% to 27%, $p < 0.05$) and an increase in alpha (from 22 to 37%, $p < 0.05$) were observed. In contrast, a small decrease in theta (from 19 to 15%, $p < 0.05$), high beta (from 8 to 7%), gamma (from 5 to 4%) was observed, and no change in low beta (10%, $p < 0.05$), was monitored.

On the other hand, after tDCS, an increase (not significant) in each band was observed, but a frequency-specific increase like tACS was not observed. As far as the percentage distribution is concerned, there is not much difference before and after. Only a small change was observed in delta (38% to 39%, $p < 0.83$), alpha (20% to 19%, $p < 0.15$), but no change in theta (19%, $p < 0.33$), low beta (10%, $p < 0.39$), high beta (8%, $p < 0.96$), and gamma (6%, $p < 0.13$) was shown.

IV. Discussion

In this study, fNIRS and EEG were employed simultaneously to investigate electrical stimulation effects in the brain, i.e., the effects of two typically used tES protocols in HD configuration over the PFC. The use of the same neurophysiological readout (i.e., fNIRS) is a critical condition that allows one to directly compare the effects of distinct stimulation modalities, which are seldom used together with EEG for modulation-based setups. More specifically, we performed fNIRS to investigate the manner whether tES applied symmetrically over the PFC modulates the resting-state activity during and after the electrical stimulation in healthy adults. We observed that both tDCS and tACS increased hemodynamic activity, albeit slightly differently.

One hypothesis is that tDCS and tACS would cause PFC activation during the resting state. We expected the hemodynamic responses to increase as compared with the baseline (before stimulation). The results of the current study support this hypothesis. The PFC was modulated after intervention and exhibited an increase in the ΔHbO response and a decrease in the ΔHbR response with tDCS, whereas the same response caused by tACS was slightly lower in magnitude. This result is different from the previous finding reported in fMRI literature, where the BOLD signal was not attenuated by the application of alpha tACS during rest [75]. This may be due to the areal difference of stimulation electrodes on the visual cortex rather than on the PFC, as in this study. Another explanation is that the visual cortex is dominated by alpha oscillations, and the BOLD signal is assumed to be negatively correlated with its power [76]. This suggests that cortical targeting can be achieved not only by selecting appropriate electrode montages, but also by selecting stimulation frequencies [77]. Moreover, tACS induces changes in brain activity differently than tDCS [78]. Such studies generally imply that either the manipulation of the baseline BOLD signal is extremely small that it cannot be detected by fMRI, or an existing BOLD response is more easily manipulated than resting activity. Based on the former notion, a regional cerebral blood flow and the concentration of oxygenated blood can be manipulated by tDCS, as measured using positron emission tomography after stimulation during rest, and during stimulation using fNIRS [40], [79], [80].

After the stimulation period, the mean alpha power increased significantly during rest because of a 10 Hz tACS. This result is consistent with a previous study, where power increase at the individual alpha frequency due to tACS lasted for 70 min [68], [69]. In another study, significant after-effects of 10 Hz tACS on alpha activity were not observed, likely due to the task performance associated with tACS. Furthermore, a 10 Hz tACS can cause entrainment because it is the intrinsic frequency that causes entrainment effects [78], which are supposed to be the underlying mechanism (plasticity) for after-effects [81]–[83]. Meanwhile, a low-beta band increase was observed but not investigated in this study. This phenomenon has been reported previously in the application of gamma tACS [84]. It may be caused by enhancement in the low-beta frequency band due to its proximity to the alpha range. However, the neuromodulatory effects induced by tDCS remains inconclusive due to the different analysis approaches, differences in measurement acquisitions, and stimulation parameters such as current intensity, stimulation time, electrode sizes, and montage. Several works have been done in the past to address these issues in their capacity [26], [29]–[31], [35]–[38]. It has been demonstrated experimentally that neurons respond to tDCS-induced membrane polarization changes, thereby resulting in an increase in spontaneous neuronal firing rates after anodal tDCS [85]. We hypothesized an increase in all frequency bands due to tDCS. The powers of EEG delta, theta, alpha, low-beta, high beta, and gamma bands increased but not significant after the

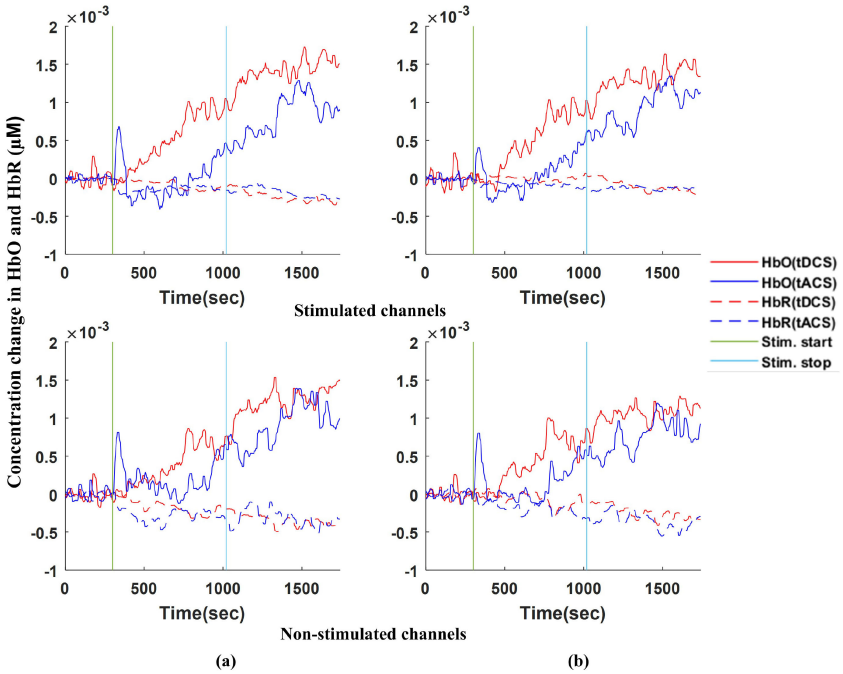

Fig. 6. Mean hemodynamic responses of stimulated and non-stimulated channels with HD-tACS/tDCS: (a) Right PFC and (b) left PFC. The hemodynamic mean was a little less in non-stimulated channels: In the tDCS case, the mean hemodynamic of stimulated ones is (a) 7.8739e-4 and (b) 7.3576e-4, whereas non-stimulated one has (a) 6.5309e-4 and (b) 6.0509e-4. Similar behavior is observed in the tACS case.

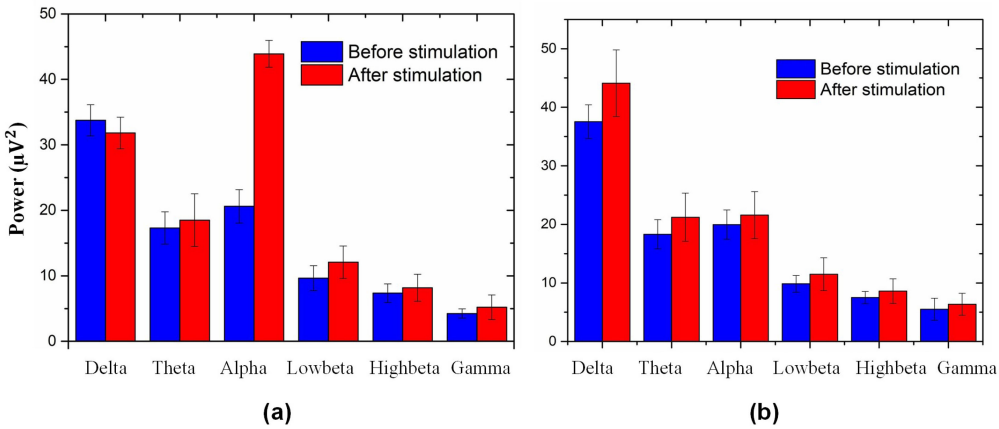

Fig. 7. Band-wise comparison of EEG powers before and after (a) HD-tACS and (b) HD-tDCS. Significant (magnitude ≈ 22, $p < 0.01$) increase in alpha and low beta (magnitude ≈ 4, $p < 0.05$) power is observed in HD-tACS. The visible increase but not significant in all band powers can be viewed in HD-tDCS.

stimulation period. This finding can be explained by the fact that tDCS disrupts the equilibrium of both excitatory and inhibitory neurons, thereby inducing an increase in specific band activity either at the beginning or after stimulation. The increase in most frequency band was reported in the literature during deep brain stimulation [86]. The increase in alpha band power after anodal stimulation confirms the results of Spitoni *et al.* [87], Roy *et al.* [88] and Kim *et al.* [84]. These results might be consistent with the notion that tDCS increases neural efficiency in brain dynamics and in patients with mild cognitive impairment [89]–[92]. Hence, tDCS might facilitate the activation/deactivation of the medial PFC during the accomplishment of cognitive tasks, thereby affording better performances [93]. On the contrary, the percentage band-wise power distribution is contrasting to the results of mean band powers. No significant difference was observed before and after tDCS stimulation. Because the change caused by stimulation will uniformly be increased in the individual band powers. Moreover, a small increase after tDCS appeared while comparing mean band powers of individual bands (Fig. 7).

tES-induced changes might occur primarily in the areas under the stimulating electrodes. However, the distant electrodes in an HD configuration should be investigated to obtain more information, as performed in this study. The cathodes located slightly far from the anode indicated less hemodynamic changes in the corresponding channels. However, both hemispheres were

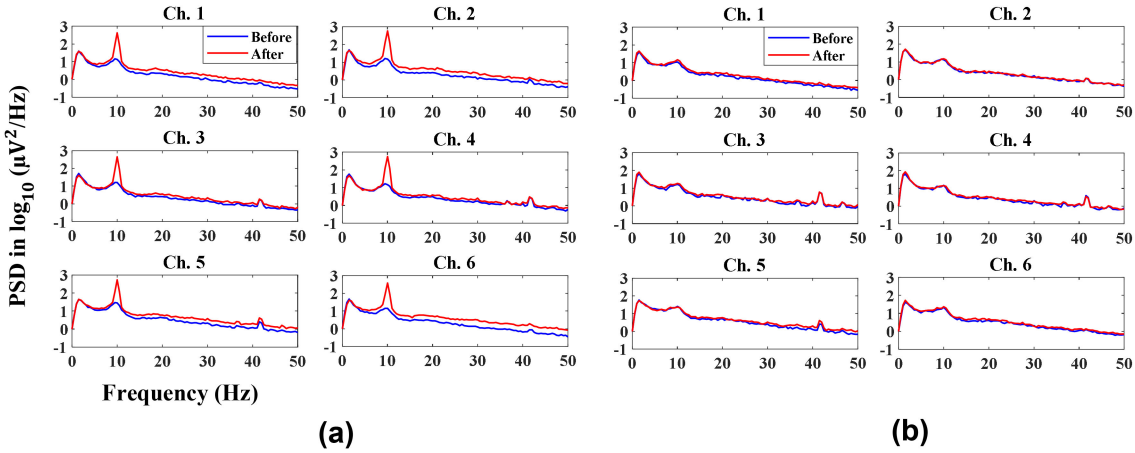

Fig. 8. Comparison of PSD of EEG channels 1-6 before and after (averages of 15 subjects): (a) HD-tACS and (b) HD-tDCS. tACS shows increases in specific frequencies, while tDCS shows increases in all frequencies. The entrainment effect due to tACS at 10 Hz can be observed in all channels.

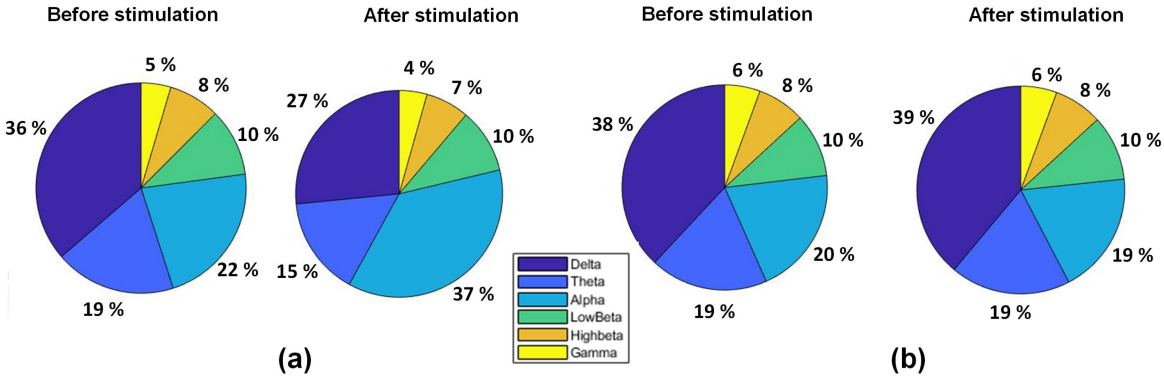

Fig. 9. The difference in band-wise power distribution of EEG channels before and after (a) HD-tACS and (b) HD-tDCS. The 15 % increase in alpha and 9% decrease in delta band are observed in the tACS case. However, very less changes can be seen in tDCS because the distribution of power in each band with respect to the total power remains the same.

simultaneously targeted. As reported in an earlier study, if stimulation was provided in one hemisphere, then the effect of the other hemisphere was less [40]. tES combined with neuroimaging methods is likely to benefit the identification of stimulation parameters that modulate relevant brain substrates for augmenting specific oscillations and hemodynamics that could be associated with cognitive improvement as reported in the literature [23], [30], [99].

A. Confounding Factors

The application of tACS has been reported to produce phosphene via retinal stimulation [94], [95]. This phenomenon can be a distractor, thereby reducing attention and affecting the results of task-based studies [96]. This effect would apply to both areas near the eyes, as reported by all the subjects in this study during tACS but not during tDCS. Antal *et al.* [97] reported that transcranially apply direct currents can produce artifacts in the echo planar imaging signal on the scalp and in the cerebrospinal fluid. However, under the same conditions, 10 Hz tACS did not yield significant artifacts [98]. It can be concluded that the fNIRS signals measured are unlikely to be affected significantly by stimulation artifacts, but not in the case of EEG. Hence, the results of tACS measured via EEG during stimulation were not analyzed in this study.

B. Limitations and Future Studies

Overall, tDCS and tACS induced modulation within the PFC region, as simultaneously measured via EEG and fNIRS. However, the results of this study must be interpreted with caution because of some limitations. Changes in brain activity might occur because of behavioral or physiological confounders. In one subject, tACS delivery was disrupted due to high impedance. This subject's data may have affected the results because fNIRS signals got corrupted due to on/off stimulation on several occasions. Therefore, we excluded this subject's data in the analysis. Despite these limitations, this exploratory study demonstrated the feasibility of concomitant tES and hybrid fNIRS–EEG. We delivered tACS at the alpha frequency; however, we did not consider the individual alpha peak frequency. Other frequency bands in hybrid combinations should be included in future studies. Another limitation is the lack of computational modeling of the electric field distribution for tES that should

be considered in future studies [31], [35], [46], [47]. Other limitations of the present study must be addressed in future studies. Owing to the limited number of fNIRS measurement channels, we restricted our analysis to the frontal cortex to obtain the overall effect of tES. However, additional EEG channels were not used such that an unfair analysis can be prevented, as the purpose was to demonstrate the usage of both modalities simultaneously for the same brain region. In the future, the simultaneous measurement of the frontal area and the entire head, enabled by adding more fNIRS channels, might be performed to obtain better connectivity measures of the PFC with other brain areas [99]. The development in user-friendly stimulation protocols combined with imaging techniques can be monitored at home by the end-users for neurorehabilitation, especially during the pandemics [100]–[102]. In this study, modified existing and developed electrical noise removal methods from the EEG data were adopted [103], [104]. Even after applying such methods, some fluctuations remain in different channels that were not consistent among subjects. It was unclear whether such fluctuation was due to the presence of the electrical component or from the brain. Therefore, we did not report the stimulation period data of EEG. In the future, we will improve the noise removal method and apply it to the same EEG data to confirm entrainment effects due to 10 Hz stimulation. The spatial resolution of fNIRS is lower than that of fMRI, which is problematic. This disadvantage can be overcome in the future by applying dense optode configurations for measurements [105], [106]. The sample size of this study is modest however, it is comparable with those of other neuroimaging studies in the field [40], [44], [49]. Owing to this limitation, the statistical power can be affected. A larger number of subjects with greater statistical power may be considered in future studies. Finally, gender-based variability was not assessed as same-gender participants were recruited in the present study. In future studies, both genders will be recruited to verify the neuromodulatory effect of tES.

V. Conclusion

In summary, we discovered increased prefrontal activity caused by tES measured using fNIRS and EEG. Stimulation was applied concomitantly with fNIRS and EEG acquisition in the resting state. Significant improvements in mean hemodynamic responses during and after stimulation periods caused by tDCS and tACS were observed. The between-group comparison revealed significantly less mean hemodynamic responses caused by tACS compared with tDCS. We demonstrated the feasibility of a high-density configuration in increasing the hemodynamics in both hemispheres simultaneously through not only tDCS, but also with tACS. Moreover, an increase in alpha band power and a low beta band power were observed after the tACS stimulation. Although tDCS is not frequency-specific, it affected most bands significantly. These findings suggest that both sides of the PFC can be targeted and that tACS/tDCS stimulation techniques are equally effective in HD configurations, which may be of clinical relevance. These results can be further improved and used in clinical procedures for the treatment of patients with mental disorders.

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