

Experimental-design Specific Changes in Spontaneous EEG and During Intermittent Photic Stimulation by High Definition Transcranial Direct Current Stimulation

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Abstract—Electroencephalography (EEG) as a biomarker of neuromodulation by High Definition transcranial Direct Current Stimulation (HD-tDCS) offers promise as both techniques are deployable and can be integrated into a single head-gear. The present research addresses experimental design for separating focal EEG effect of HD-tDCS in the ‘4-cathode × 1-anode’ (4 × 1) montage over the left motor area (C3). We assessed change in offline EEG at the homologous central (C3, C4), and occipital (O1, O2) locations. Interhemispheric asymmetry was accessed for background EEG at standard frequency bands; and for the intermittent photic stimulation (IPS). EEG was compared post- vs pre-intervention in three HD-tDCS arms: Active (2 mA), Sham (ramp up/down at the start and end), and No-Stimulation (device was not powered), each intervention lasting 20 min. The asymmetric background EEG changes were only in the central areas with right-side amplitude spectra prevalence, most pronounced in the no-stimulation arm, where they depended on comparison time-points and were consistent with markers of transition between drowsiness and vigilance – bilateral decrease in the delta and asymmetric central increase in the alpha and beta1 bands. For the active arm, similar but less pronounced changes occurred in the alpha band. In contrast, responses to IPS developed similar asymmetric amplitude increase at four harmonics of the IPS of 3 Hz *only* in the active arm, against a background of a brain-wide symmetric increase in both active and sham arms. Our protocols and analyses suggest methodological caveats for how EEG of tDCS studies could be conducted to isolate putative brain polarization outcomes. © 2019 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: transcranial direct current stimulation (tDCS), electroencephalography (EEG), Intermittent photic stimulation, EEG photic driving.

INTRODUCTION

Even as trials of transcranial direct current stimulation (tDCS) for clinical rehabilitation and cognitive enhancement progress (Brunoni et al., 2012; Bikson et al., 2016; Antal et al. 2017; Baudewig et al., 2018; Brunelin et al., 2018; David et al., 2018; Osoegawa et al., 2018), questions remain about the most robust biomarkers of neuromodulation, including application-specific target engagement (Bikson et al., 2018). The

use of electroencephalography (EEG) with the application of tDCS is compelling mechanically, as both techniques integrate into a single head-gear (Woods et al., 2016); and biophysically, through the principle of reciprocity (Dmochowski et al., 2017). Measurement of EEG “online” during tDCS is complicated by inherent artifacts (Gebodh et al., 2019). Several trials have measured EEG “offline” comparing post- to pre-tDCS (Fregni et al., 2006; Zaehle et al., 2011; Faria et al., 2012; Maeoka et al., 2012; Auvichayapat et al., 2013; Schestatsky et al., 2013; Castillo-Saavedra et al., 2016; Liu et al., 2016; Kang et al., 2018), including one trial testing changes by a sham protocol (Holgado et al., 2018). High Definition transcranial Direct Current Stimulation (HD-tDCS) is advantageous over conventional sponge-pad tDCS since HD-tDCS allows for seamless mechanical integration (both techniques use gel cups, with no risks of saline leak-

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Abbreviations: BGR, background; EEG, electroencephalography; HD-tDCS, High Definition transcranial Direct Current Stimulation; IPS, intermittent photic stimulation.

ing as with sponge-pads) and for focal stimulation using stimulation montages like the ‘4-cathode × 1-anode’ (4 × 1) ring (Datta et al., 2008; Caparelli-Daquer et al., 2012; Edwards et al., 2013; Kuo et al., 2013).

Any study of EEG changes by tDCS is limited by technical implementation (e.g. stimulation and recording hardware interactions (Gebodh et al., 2019); but also experimental design; the latter is addressed in detail here. In this exploratory study, we examined neurophysiological outcomes that indicated topographically restricted (focal) effects of HD-tDCS on EEG, namely locations inside and outside the stimulation region. In addition to background EEG, intermittent photic stimulation (IPS) evoked EEG responses were assessed, which can reveal latent bioelectrical oscillators not present or weak in spontaneous EEG during resting state (Lazarev et al., 2001). Our objective was not to identify explicit EEG responses to tDCS but to explore methodological issues surrounding the reproducible detection of real changes in EEG including: the validity of traditional sham approaches, the comparison of background EEG vs. IPS, the consideration of multiple time-points and EEG frequency bands, and the use of focal HD stimulation to resolve emergent asymmetries.

EXPERIMENTAL PROCEDURES

Participants

Twenty-five healthy individuals (eight males) aged 20–57 years (mean ± SD: 33.6 ± 11.1) with no history of neurological, psychiatric, chronic or drug-related illness volunteered for the study, without financial compensation. Subjects included, but were not limited to, staff and students at the Fernandes Figueira Institute and the Hospital Universitário Gaffrée e Guinle. All subjects underwent neurological and psychiatric evaluations by a neuropsychiatrist through an oral interview and physical examination. Subjects were medication free and had no implanted electrical devices or intracranial implants. The study was approved by the Ethics Committee of the Hospital Universitário Gaffrée e Guinle of the Federal University of the State of Rio de Janeiro (HUGG UNIRIO). All individuals gave written informed consent and received no compensation.

Experimental design

The study consisted of three intervention conditions (arms). These included “Active” HD-tDCS (20 participants), “Sham” HD-tDCS (14 participants), and “No-stimulation” HD-tDCS (13 participants). Several subjects participated in more than one condition (stimulation arm) with a minimum wash-out interval of 2 days. Across all experimental conditions, subjects remained comfortably seated with their eyes closed, and were instructed to remaining awake, while EEG was monitored to ensure a waking state was maintained. During the experimental procedure, spontaneous background (BGR) EEG was acquired prior to (BGR1, 3 min), during (4 min), and after (BGR2, 3 min) IPS (at 3, 5, 10 and 21 Hz). The intervention arm was then

applied for 20 min, utilizing either active HD-tDCS, sham HD-tDCS, or no-stimulation HD-tDCS. EEG was then acquired after the intervention arm, prior to (BGR3, 3 min), during (4 min), and after (BGR4, 3 min) IPS (Fig. 1A). Here *spontaneous BGR EEG* indicates EEG acquired in the absence of photic or electrical stimulation (HD-tDCS).

HD-tDCS

In all conditions, Ag/AgCl sintered electrodes were used for electrical stimulation (tDCS) and were inserted into gel-filled plastic holders (High Definition electrodes – Minhas et al., 2010) arranged in a ‘4-cathode × 1-anode’ (4 × 1) configuration. The central anodal stimulation electrode was placed on the left hemisphere over standard EEG location C3 (International 10/20 System) and the remaining four cathodal stimulating electrodes were placed in 5-cm radius around the anode (Datta et al., 2009). Stimulation current was supplied with a 4 × 1 stimulation set-up consisting of a 1 × 1 current generator connected to 4 × 1 adaptor (Soterix Medical Inc., New York, NY, USA).

During the active HD-tDCS intervention arm, 2 mA of current was applied over 20 min including 1-min ramp-up and ramp-down periods. In the sham HD-tDCS intervention arm, current ramped up to 2 mA then down, only during the first and the last minutes of the intervention period (without stimulation during the remaining 18 min). In the no-stimulation intervention arm, the stimulation electrodes were placed at their respective locations, however the stimulation device was not powered on.

EEG recording and IPS

EEG signals were acquired with a 32-channel Bio-logic Ceegraph device (Bio-Logic Systems Corp.) at 8 scalp locations. In the left hemisphere, the recording electrodes were arranged according to the HD-tDCS electrode positions. Three of them were placed inside the stimulated area. The central position (C3) corresponded to anode; the posterior central position (C3p, rearwards and to the right from the anode) in the “outer ring” of HD-tDCS corresponded to cathode; and the intermediate position, 3 cm anteriorly from the anode (C3a), was between stimulation electrodes. The recording electrode outside the stimulated area was placed in the left occipital region (O1). In the anode and cathode positions, the recording and stimulation electrodes replaced each other before and after HD-tDCS. In the right hemisphere, which was not electrically stimulated, the recording electrodes were positioned in the homologous points C4, C4p, C4a, and O2. Acquired data were online referenced to the linked earlobes, sampled at 512 Hz, and bandpass filtered between 0.3 and 70 Hz with line noise suppression at 60 Hz.

EEG was acquired before and after each experimental intervention arm. Prior to each intervention, EEG was acquired for 10 min, which included 3 min resting EEG before, 4 min during, and 3 min after IPS. This

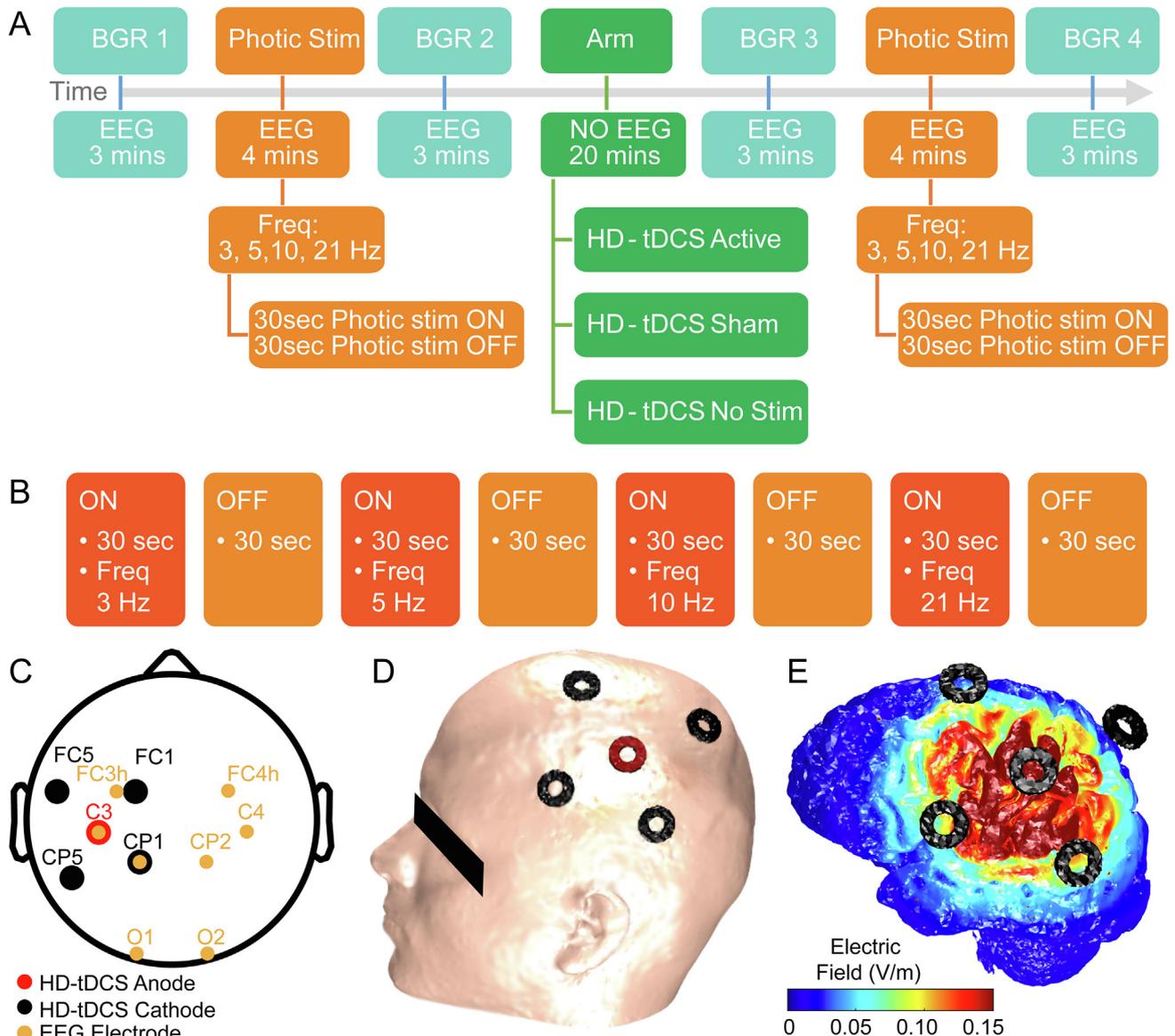


Fig. 1. Study overview, photic stimulation procedure and stimulation and recording montage. **(A)** EEG was acquired prior to (BGR1; 3 min), during (4 min), and after (BGR2; 3 min) photic stimulation (at 3, 5, 10, 21 Hz). The intervention arm was then applied (20 min) with no accompanying EEG, utilizing either active-HD-tDCS, sham-HD-tDCS, or no-stimulation-HD-tDCS. EEG was then acquired after the intervention arm, prior to (BGR3; 3 min), during (4 min), and after (BGR4; 3 min) photic stimulation. **(B)** During the periods of photic stimulation, the stimulus was presented in 30-s on and 30-s off periods at 3, 5, 10, and 21 Hz. **(C)** Stimulation and recording montage. **(D)** Model of stimulation electrode placement on the scalp in a 4 × 1 configuration with a center anode (red ring) and surrounding cathode (black rings). **(E)** Computational FEM model showing stimulation electric field on the brain with a center anode and surrounding cathodes in a 4 × 1 montage.

acquisition procedure was repeated after each HD-tDCS intervention. IPS consisted of 30-s on, 30-s off visual stimulation procedure at 3, 5, 10 and 21 Hz (4 min total; Fig. 1B). The IPS lamp (photic stimulator Nihon Kohden 4418 K – LS-701B – a xenon lamp with flash duration of less than 20 μs) was positioned at a distance of 25 cm from the eyes, with dim surrounding light.

Data analysis

EEG data were analyzed offline with Brainsys (Neurometrics, Moscow, Russia). Low frequency

movement artifacts were suppressed by high-pass filtering at 0.3 Hz. Short EEG fragments containing excessive eye or muscle movements (total duration less than 7-s) were removed manually from ongoing EEG signal during post-recording visual inspection prior to further analysis.

EEG data were epoched into 2-s bins and subjected to spectral analysis (Fourier transform). Amplitude spectra for each of the BGR periods were estimated across five frequency bands: delta (2–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta1 (13–20 Hz) and beta2 (20–30 Hz). For the IPS, EEG was examined at the frequencies of

photic stimulation (3, 5, 10, and 21 Hz) and all IPS harmonics up to 30 Hz. The parameters calculated for three central electrodes of each hemisphere were averaged and the result was considered as representing the polarized area of the left (C_L) or homologous not polarized area of the right (C_R) central region.

The changes in EEG amplitude spectra after intervention in relation to the state before (percent change) were compared in the four above-mentioned areas of the two hemispheres. For the central region, interhemispheric comparisons were performed for the averages of the three leads in the treated left central area (C_L), which represented its anode, cathode, and intermediate parts; and homologous averages of the non-treated right area (C_R). For the occipital region, the data for the left (O1) were compared to those on the right (O2).

For the BGRs, each pre-intervention background EEG before (BGR1) and after (BGR2) IPS was compared with both post-intervention backgrounds (BGR3 and BGR4, respectively). Similarly, the data for BGRs recorded after IPS were compared with those before IPS, for both pre- and post-intervention states. The EEG during IPS, before, and after intervention were compared for each photic stimulation frequency. The putative interhemispheric asymmetry in these changes was considered as a principal criterion of focality of an intervention effect since the structure of intact EEG is usually most similar between the homologous cortical points, whereas the differences between EEG of anterior and posterior areas have a great inter-individual variability (Niedermeyer and Lopes da Silva, 2005).

To visualize hemispheric changes, topographically, across conditions and frequency bands, the EEGLAB toolbox (Delorme and Makeig, 2004) and the gramm toolbox (Morel, 2018) in MATLAB (R2018a; MathWorks, Natick, MA, USA) were utilized. Central (C3 and C4) and occipital (O1 and O2) recording electrodes were mapped to standard points, whereas central anterior (C3a, C4a) and central posterior (C3p, C4p) recording points were mapped to their closest standard points namely FC3h (for C3a) and FC4h (for C4a) for anterior, and CP1 (for C3p) and CP2 (for C4p) for posterior (odd numbers correspond to the left hemisphere and even numbers to the right hemisphere; Fig. 1C). These points were used to construct a low-density topographic scalp map of the percent change in spontaneous background EEG amplitude spectra. Points of similar change were indicated with isometric lines. Visualization of the stimulation electrode placement on the scalp (Fig. 1D) as well as electric field distribution on the brain (Fig. 1E) was achieved with the ROAST toolbox (Huang et al., 2018, 2019), which utilized a 1 mm^3 T1-weighted MRI scan.

In this exploratory research, statistical significance of the post-intervention changes in each area and of the interhemispheric asymmetry in these changes was evaluated by the non-parametric Wilcoxon signed-rank test. Only temporal dynamics of the EEG parameters in a group of the same intervention conditions were considered. The groups were not compared among themselves.

RESULTS

No-stimulation condition: background EEG

For the comparison of the BGR2 with BGR3, a 20-min intervention with no current resulted in an increase in central area of alpha and beta1 amplitude spectra (30–36% increase C_L and C_R in the alpha band, $p < 0.01$; 8% C_R in the beta1 band, $p = 0.02$) with emergence of right-biased asymmetry in the central areas in the theta ($p = 0.02$), alpha ($p = 0.02$) and beta1 ($p = 0.02$) bands (Fig. 2). In the occipital leads, from BGR2–BGR3, a pronounced amplitude increase without asymmetry was observed in the alpha ($p < 0.01$, 52–55%) and beta1 bands ($p < 0.01$, 18–20%).

For BGR2–BGR4, right-biased asymmetry emerged in the central areas in the alpha ($p = 0.03$) and beta1 ($p = 0.04$) bands, with symmetrical increase in the alpha band in occipital areas ($p < 0.05$, 23–28%).

There was significant reduction in the delta amplitude spectra in the central areas of both hemispheres for BGR2–BGR3 and BGR2–BGR4 ($p < 0.01$, 15%, and $p < 0.05$, 10%, respectively). The results emphasize the possibility of complex (e.g. asymmetric, frequency and location specific) changes in background EEG simply by time, which would be superimposed or even interact with active/sham stimulation induced changes.

In the pre-intervention period, EEG data from BGR1 to BGR2 showed significant increase in delta amplitude spectra ($p < 0.02$, 10–17%) in all the four areas and reduction in the alpha and beta1 bands in the occipital areas ($p < 0.02$, 11–19%).

Active HD-tDCS: background EEG

In a comparison-period specific manner, hemispheric and frequency specific changes in background EEG are observed (Fig. 3). For example, depending on the comparison time (BGR1–4 vs BGR2–3) a decrease or increase in frequency-specific activity were observed. These differences highlight the importance of careful consideration of the role of measurement periods around the stimulation intervention time.

Changes in background EEG following 20 min of active HD-tDCS for BGR2–BGR3 (Fig. 2) were less pronounced (in % values) and symmetrical compared to the no-stimulation arm; with the exception of an emergent asymmetry ($C_R > C_L$) in the beta2 band ($p < 0.04$) that was not accompanied by significant changes in overall amplitude spectra compared to the pre-intervention state. Taken in isolation, the emergent focal frequency-band specific asymmetry would be consistent with focal brain polarization by active HD-tDCS, however the myriad of changes in the no-stimulation arm qualify confidence in this effect. Similarly, active HD-tDCS generally increased alpha ($p < 0.05$ for all areas, 12–21%) and beta1 ($p < 0.02$ for all areas, 6–15%) activity, the percentage being higher in the occipital areas (Fig. 2). That said, confidence in this time-point specific outcome is mitigated by comparable changes in no-stimulation and especially sham-stimulation conditions, as is confidence

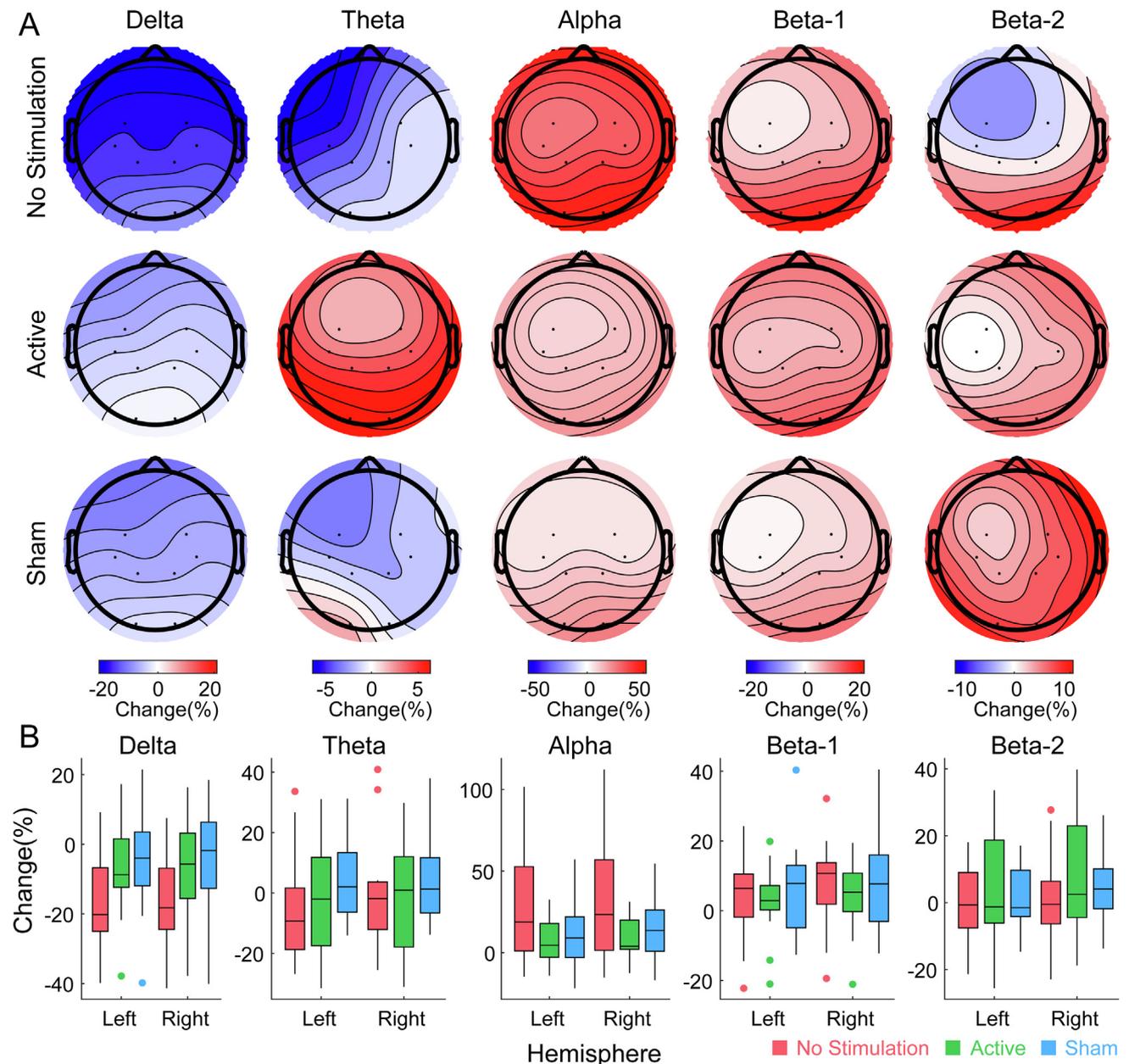


Fig. 2. Grand average percent change in spontaneous background EEG amplitude spectra comparing BGR2–BGR3, across each of the three intervention periods (no-stimulation HD-tDCS, active HD-tDCS, sham HD-tDCS). For each intervention, comparisons are made for delta, theta, alpha, beta1 and beta2 frequency bands. **(A)** Percent change was only available at the points indicated on each scalp map and isometric lines indicate areas of similar change. **(B)** Boxplot comparison between central left (C_L) and central right (C_R) hemispheric changes between differing stimulation conditions, across indicated EEG frequency bands. Central left and central right hemispheric activity are composed of the averages of locations FC3h, C3, and CP1 for the left hemisphere and locations FC4h, C4, and CP2 for the right hemisphere. Boxplot vertical bars indicate the maximum and minimum values, and outliers are indicated with dots.

in the specificity of other active HD-tDCS findings. For example, right-side prevalence and scalp-wide increase (7–14%) in the alpha band appeared only for BGR2–BGR4 ($p < 0.05$) with no other change symmetric or otherwise for this comparison. For the BGR1–BGR3, there was amplitude spectra increase in the delta and theta bands ($p < 0.05$, 4–8%) in all the areas accompanied by central right-side delta ($p = 0.03$) and beta2 ($p = 0.02$) prevalence.

Sham HD-tDCS: background EEG

The EEG effects of sham HD-tDCS, with ramp up and down at both the start and end of the 20-min period, were qualitatively comparable to those of active HD-tDCS, with less similarities to the no-stimulation arm and a lack of interhemispheric asymmetry in amplitude spectra changes for the most of comparisons and bands (Fig. 2). Similar to the no-stimulation arm, only for the BGR2–BGR3, sham HD-tDCS led to a right-side central

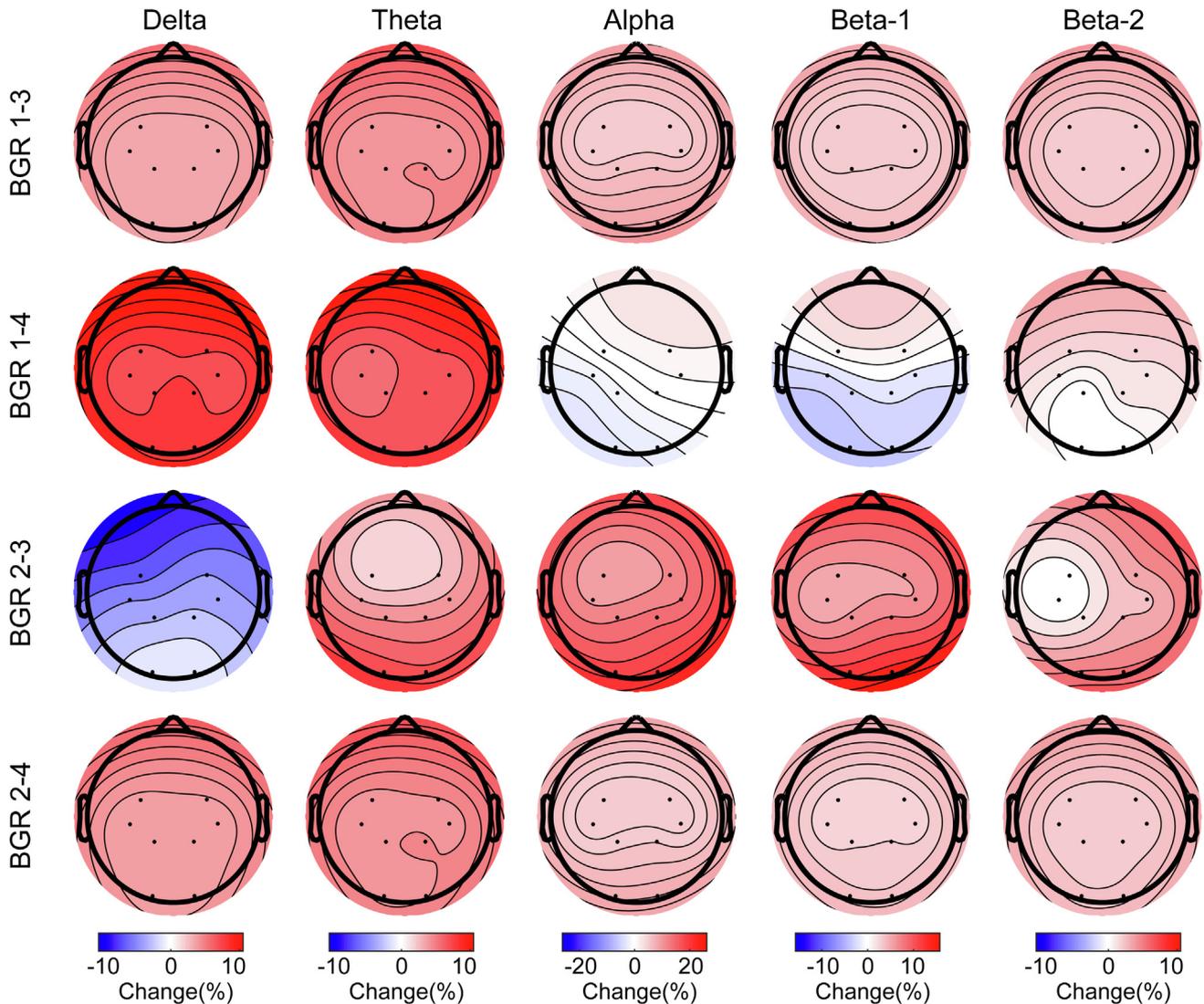


Fig. 3. Grand average percent change in spontaneous background EEG amplitude spectra comparing different time periods (BGRs), after the active HD-tDCS intervention period. For each background comparison delta, theta, alpha, beta1, and beta2 frequency bands were examined. Percent change was only available at the points indicated on each scalp map and isometric lines indicate areas of similar change.

prevalence in the beta1 band ($p = 0.04$), and in the same way was accompanied by increase in beta1 band amplitude spectra ($p < 0.05$) in O1 and O2 (10–11%) and C_R (5%). For sham HD-tDCS, no significant change in amplitude spectra was observed in any other band or lead for any other comparison (Fig. 2).

No-stimulation condition: IPS

The no-stimulation condition had no significant effects on interhemispheric asymmetry in EEG response to photic stimulation, at any time period and for any frequency and harmonics of the IPS (Fig. 4). Lack of asymmetric changes in IPS EEG is in contrast to diverse changes in background EEG following the no stimulation condition.

Active HD-tDCS: IPS

Active HD-tDCS produced a broad increase in driving responsiveness to IPS of 3 Hz. Increases were significant at the harmonics of this frequency in all areas

registered at 9 Hz ($p < 0.01$, 30–34%), except for C_L at 3 Hz ($p < 0.01$, 12–13%) and 6 Hz ($p < 0.05$, 8–13%), and C_R at 24 Hz ($p = 0.04$, 11%).

Consistent with the goal of focal polarization, the active HD-tDCS produced an asymmetric increase of the EEG photic driving response to the IPS of 3 Hz across the central areas (Fig. 4), with significant right-side amplitude prevalence at the fundamental frequency (3 Hz; $p = 0.01$) and at the 2nd (6 Hz; $p = 0.01$), 3rd (9 Hz; $p = 0.05$), and 8th (24 Hz; $p = 0.04$) harmonics (Fig. 4).

No asymmetry was observed in the occipital areas. No asymmetry in the driving amplitude changes was found during IPS of other frequencies.

Sham HD-tDCS: IPS

The sham HD-tDCS resulted in a broad trend to increase responsiveness to IPS intervention, qualitatively similar to active HD-tDCS, however increased amplitude was only

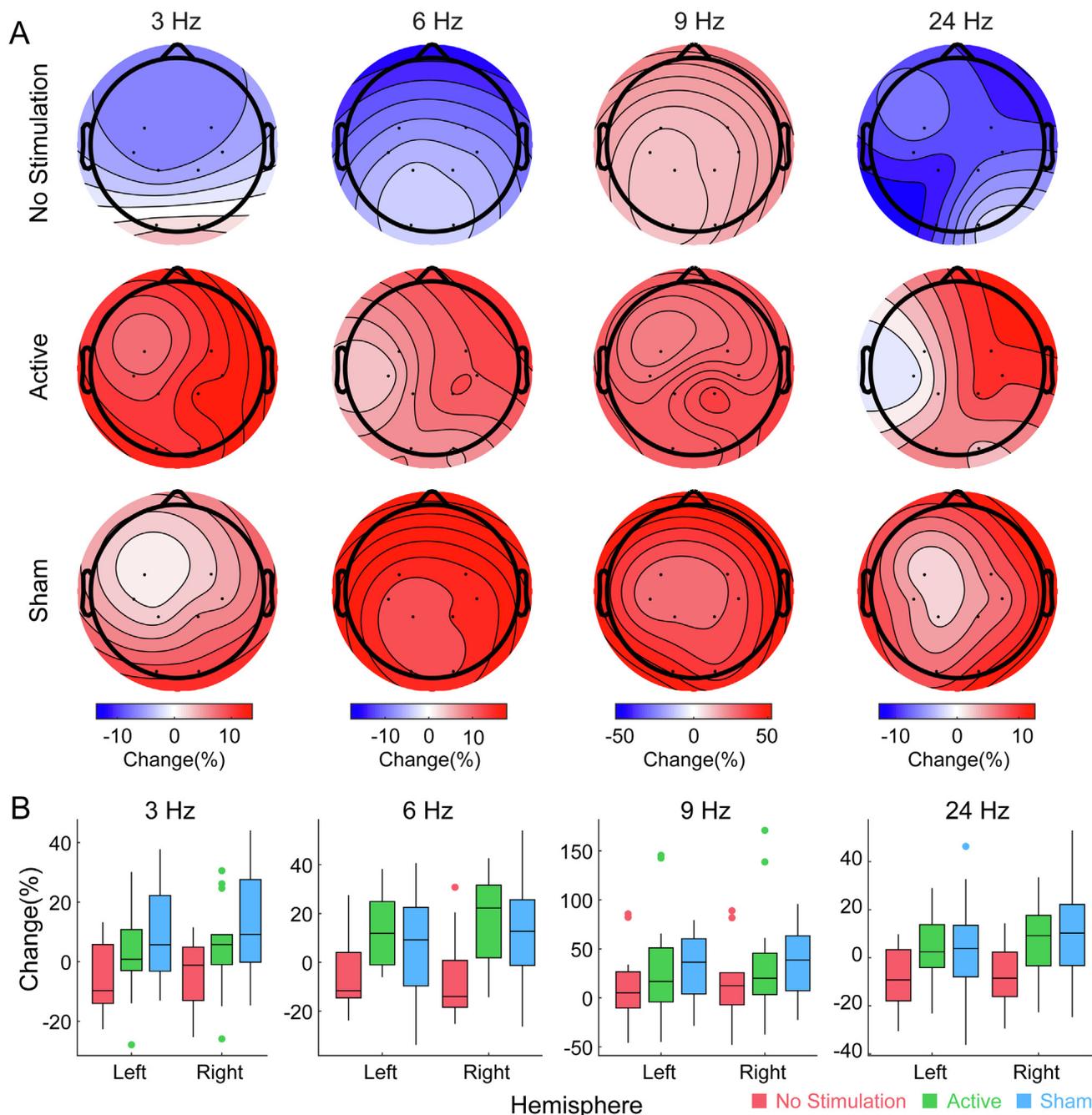


Fig. 4. Grand average percent change in EEG amplitude spectra after intervention (% in relation to the same parameters before intervention) in photic driving response to IPS of 3 Hz at the EEG frequencies corresponding to fundamental (3 Hz), 2nd (6 Hz), 3rd (9 Hz), and 8th (24 Hz) harmonics of stimulus (see Fig. 1). **(A)** Topoplots indicate the percent change across photic stimulation at harmonic frequencies for each current stimulation condition. Topoplots locations were only available at the points indicated on each scalp map and isometric lines indicate areas of similar change. **(B)** Boxplot comparison between central left (C_L) and central right (C_R) hemispheric changes between differing current stimulation conditions, across indicated EEG frequencies. Central left and central right hemispheric activity are composed of the averages of locations FC3h, C3, and CP1 for the left hemisphere and locations FC4h, C4, and CP2 for the right hemisphere. Boxplot vertical bars indicate the maximum and minimum values, and outliers are indicated with dots.

significant in response to 3 Hz IPS specifically at the EEG frequency of 6 Hz ($p < 0.05$ in all leads except for O1, 15–17%) and 9 Hz ($p < 0.05$ except for C_L , 36–52%). There was no emergent asymmetry in IPS response with sham HD-tDCS.

DISCUSSION

Across intervention arms (active HD-tDCS, sham HD-tDCS, and no stimulation HD-tDCS), distinct effects on EEG were observed specific to temporal comparisons,

regions, and frequency bands. Analysis of the HD-tDCS outcomes illustrate that the selection of comparison windows, in this case differing BGR EEG periods, can sway statistical tests (alpha/beta error). This exploratory analysis is not intended to draw definitive conclusions about temporal interactions (present in all arms) with perceptible low-dose (sham arm) or high-dose (active arm) interventions but highlights methodological issues that can confound any EEG-tDCS trial.

Results in the no-stimulation arm demonstrate nuanced (e.g. frequency and region specific; generalized or regional asymmetric) changes in background EEG over time. Such changes would be specific to overall experimental design, e.g. drowsiness/alertness, subject coaching, time span, etc.; and would overlay any real effects of active or sham stimulation conditions. For example, effects of active or sham HD-tDCS could be interpreted as reversing time related increases in alpha and decreases in delta bands together with a right-side alpha prevalence corresponding to the well-known patterns of drowsiness-to-wakefulness transition (Lindsley, 1960; Butler and Glass, 1974; Santamaria and Chiappa, 1987; Hiroshige and Dorokhov, 1997; Lazarev, 2006).

Sham (current ramp up-down) outcomes in background EEG were distinct from the no-stimulation arm and can reflect either the perception of current or a cortical response to short current stimulation and polarization – comparison of asymmetry and other changes across conditions can provide insight into which of these mechanisms is more probable. For example, the use of focal lateralized 4×1 HD-tDCS allow analysis of emergent asymmetries across central region (C_L/C_R) which could relate to focal polarization, if they are absent in sham and no-stimulation conditions.

Compared to background EEG, EEG photic driving responses to IPS are generally less sensitive to temporal changes in neural activity and subject's state (Kaiser and Gruzelier, 1996; Lazarev et al., 2001), and thus can enhance the signal to noise ratio in detecting real electrical stimulation-related effects on EEG. Indeed, we observed no significant changes in photic driving response in the no-stimulation arm. IPS of 3 Hz after active HD-tDCS showed emergent asymmetry, specifically across the central regions ($C_L < C_R$, significant across various harmonics) consistent with a hypothesis for local polarization effects. However, diffuse symmetric increase in EEG photic driving at the lower EEG frequencies (3, 6, and 9 Hz) was also observed in the active HD-tDCS and sham arm, but not in the no-stimulation arm. This can most parsimoniously be explained as changes in vigilance towards brain-wide relative cortical inactivation which is supposedly related to amplitude synchronization of slow waves (Lindsley, 1960; Niedermeyer and Lopes da Silva, 2005; Lazarev, 2006).

The IPS of 5, 10, and 21 Hz did not reveal any focal EEG consequences of polarization. This may be caused by the functional specificity of these frequencies, however this warrants further investigation. The ability to probe for tDCS response across IPS frequencies enhances nuance. The EEG photic driving responses is

considered to be a sensitive tool for revealing latent neural oscillators and oscillatory processes not present or weak in the spontaneous EEG and enhanced by physiological resonance-like driving reaction (Lazarev et al., 2001, 2015; Niedermeyer and Lopes da Silva, 2005). It permits finer estimation of neurodynamic structures of the functional state of a brain site registered, which is composed of functionally different coexisting neurophysiological processes reflected, inter alia, in different EEG frequency components (Lazarev, 2006).

Notwithstanding the explanatory nature of the present work, we suggest important methodological qualification for past studies and consideration for future works. In this light, an application of IPS in the EEG studies of neurophysiological effects of HD-tDCS can substantially increase sensitivity and precision of the method in relation to focality than spontaneous background activity. The results obtained also show that these EEG studies must consider the appropriateness of the 'sham' design given the study goals and carefully control experiment timing and subject vigilance. Focal HD stimulation combined with topographic analyses (asymmetries) increases confidence in outcomes along with showing target engagement, which is not possible with conventional sponge-pad tDCS due to their comparative diffuse current delivery.

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