Corticospinal excitability changes to anodal tDCS elucidated with NIRS-EEG joint-imaging: an ischemic stroke study

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Abstract— **Transcranial direct current stimulation (tDCS) has been shown to modulate corticospinal excitability. We used near-infrared spectroscopy (NIRS) - electroencephalography (EEG) joint-imaging during and after anodal tDCS to measure changes in mean cerebral haemoglobin oxygen saturation (rSO2) along with changes in the log-transformed mean-power of EEG within 0.5 Hz - 11.25 Hz. In two separate studies, we investigated local post-tDCS alterations from baseline at the site of anodal tDCS using NIRS-EEG/tDCS joint-imaging as well as local post-tDCS alterations in motor evoked potentials (MEP)-measure of corticospinal excitability. In the first study, we found that post-tDCS changes in the mean rSO2 from baseline mostly correlated with the corresponding post-tDCS change in log-transformed mean-power of EEG within 0.5 Hz - 11.25 Hz. Moreover, a decrease in log-transformed mean-power of EEG within 0.5 Hz - 11.25 Hz corresponded with an increase in the MEP-measure of corticospinal excitability - found in the second study. Therefore, we propose to combine NIRS-EEG/tDCS joint-imaging with corticospinal excitability investigation in a single study to confirm these finding. Furthermore, we postulate that the innovative technologies for portable NIRS-EEG neuroimaging may be leveraged to objectively quantify the progress (e.g., corticospinal excitability alterations) and dose tDCS intervention as an adjuvant treatment during neurorehabilitation.**

I. Introduction

Transcranial direct current stimulation (tDCS) - an electrically based intervention directed at the central nervous system level - has been shown to modulate cortical neural activity and is a promising tool to facilitate neuroplasticity [1]. However, inter-subject variability and intra-subject reliability limits clinical translation where a recent meta-analyses showed that the treatment effects of tDCS in patients with stroke are rather inconsistent across studies and the evidence for therapeutic efficacy is still uncertain [2]. Here, neuroimaging may be able to objectively quantify the individual brain-state, e.g. cortical excitability alterations, during tDCS which may lend to closed-loop dosing of tDCS [3] as an adjuvant treatment to facilitate neurorehabilitation. Indeed, it is necessary to track the fluctuations in the functional state of the brain where, e.g., alpha-rhythm states may have a significant effect in perceptual learning since more than 60% of the observed inter-subject variability in perceptual learning can be ascribed to ongoing alpha activity [4]. Also, a neuroimaging method to quantify any homeostatic interaction between the task and tDCS is important to determine their relative timing, e.g., as an adjuvant treatment during motor rehabilitation [5]. Moreover, heterogeneously damaged cortical regions in stroke subjects present a challenge due to unpredictable alterations of current flow and unpredictable effects on the cortical targets, which may need online monitoring of tDCS effects with neuroimaging for driving individualized tDCS as an adjuvant treatment during neurorehabilitation [6]. Therefore, we hypothesize that neuroimaging-guided brain-state dependent tDCS [7] will lead to its better therapeutic efficacy as an adjuvant treatment in stroke rehabilitation.

Non-invasive neuroimaging techniques that have previously been combined with tDCS include electroencephalography (EEG), functional magnetic resonance imaging (fMRI), and functional near-infrared spectroscopy (fNIRS). fMRI relies on an indirect signal, the blood oxygenation level-dependent (BOLD) contrast, which is caused by an increase in oxygen delivery subsequent to increased neuronal activity. fNIRS is a relatively recent optical technology for studying brain function that measures several physiological parameters related to cerebral blood flow and oxygenation including measurements of changes in oxygenated (HbO2) and deoxygenated (HHb) hemoglobin. fNIRS presents several advantages relative to fMRI, such as measurement of concentration changes in both HbO2 and HHb [8], finer temporal resolution, ease of administration and relative insensitivity to movement artefacts. EEG - electrical potential recorded from the scalp as a measure of neural activity [9] - is due to the electric currents from excitable membranes of brain tissue that superimpose at a given location in the extracellular medium and generate the potential. While fMRI has become the gold standard for in vivo imaging of the human brain, fNIRS and EEG are more convenient and less expensive technology than fMRI.

Neural activity has been shown to be closely related, spatially and temporally, to cerebral blood flow (CBF) that

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supplies glucose via neurovascular and metabolic coupling mechanisms [10][11] where excitation versus inhibition acute effects of tDCS on the population kinetics of neural activity can produce a whole spectrum of EEG signals within the oscillatory regime [12]. The effects on the population kinetics depend on the direction of cortical current flow determining the relative influence of acute tDCS on the cellular targets responsible for the modulation of synaptic efficacy, which are primarily the neuron somata and axon terminals [13]. Therefore, not all neural tissue will be equally affected by a given stimulation protocol which may distinctly affect neuronal populations/neuronal compartments [13].

Individual differences in the neural tissue characteristics [7] as well as heterogeneously damaged cortical regions in stroke subjects with respect to the direction of cortical current flow may lead to the variability in response to tDCS [14]. Therefore, we propose concurrent neuroimaging to capture individual factors that determine this variability in response to tDCS. Towards that overarching goal, we developed and showed the feasibility of EEG-NIRS based monitoring of neurovascular coupling (NVC) during tDCS [15]. We present in this paper experimental results to elucidate the variability in corticospinal excitability changes to tDCS, especially on the lesional hemisphere, based on NIRS-EEG joint-imaging in patients with a previous ischemic stroke of the right or left middle cerebral artery. Furthermore, based on these preliminary results, we propose EEG-NIRS joint-imaging for closed-loop control of tDCS.

II. Methods

A. NVC evaluation with NIRS-EEG/tDCS joint-imaging

Simultaneous recording of NIRS and EEG was conducted on five chronic (>6 months, see Table 1) ischemic stroke survivors after obtaining informed consent from the subjects. The stroke survivors had no contraindications to non-invasive brain stimulation. The experiments have been conducted according to the principles expressed in the Declaration of Helsinki [16].

The NIRS-EEG/tDCS joint-imaging protocol was similar to that of our prior study [17]. Participants were seated in a quiet room and their eyes were open and fixed on a point on the wall in front of them during the entire experiment. PISTIM (Neuroelectrics, Spain) electrodes were placed over F3 (corresponding to the left hemisphere) and F4 (right hemisphere) of the international 10-20 EEG system, and SPONSTIM-25 (Neuroelectrics, Spain) electrodes were placed over Cz. This F3 (F4 when monitoring the right hemisphere) anodal and Cz cathodal tDCS montage was selected based on computational modeling (using StimViewer, Neuroelectrics, Spain) [15] in order to target primarily the outer convex brain territory (superficial divisions) of the superficial middle cerebral artery (MCA) territories (see Figures 1a, b). The tDCS at a current density of 0.526A/m^2 was turned ON for 30sec with 10sec ramp-up and ramp-down (see Figure 1c), which was repeated 15 times in random order with 30sec OFF periods in between for the lesional and contralesional hemispheres (ischemic stroke was restricted to a single hemisphere). Eyes-open block-averaged resting-state NIRS oximeter (INVOS Cerebral Oximeter Model 4100, USA) measurements were conducted just above each eyebrow and below the F3/F4 sites using the adult SomaSensor (SAFB-SM, INVOS, USA). The SomaSensor consists of two LED sources (730nm and 810nm) and two photodiode detectors at a distance of 3 cm and 4 cm so that the short separation NIRS signal can be regressed out from the longer separation NIRS signal in order to diminish the systemic interference [18]. Eyes-open block-averaged resting-state percent change in the mean regional cerebral haemoglobin oxygen saturation (rSO2) in the first 10 sec of ON periods, i.e. the onset response [15] [19], relative to the first 10 sec of OFF periods was measured where the baseline was set at the start of the experiment. Also, eyes-open resting-state EEG (StarStim, Neuroelectrics, Spain) was recorded at 500Hz from the nearby electrodes F1, FC3, F5, F2, FC4, F6 (international 10-20 system) with CMS/DRL electrodes placed in the left mastoid. EEG artifacts related to tDCS are possible due to issues with electrical (e.g. unknown electrode impedance changes during stimulation) and mechanical compatibility (saline from sponges shunting neighboring electrodes) where concurrent recording is possible with an optimized device (Starstim; Neuroelectrics, Spain) and rational experimental design (using PISTIM electrodes; Neuroelectrics, Spain) [20]. The raw EEG was pre-processed using EEGLAB functions (specifically, Artifact Subspace Reconstruction method) [21] where artefactual epochs were also removed following subsequent visual inspection of the data. The log-transformed mean-power of processed EEG within the 0.5Hz-11.25Hz range (selected based on our prior work [15]) from F3, F1, FC3, F5 were averaged for left hemisphere and from the F4, F2, FC4, F6 were averaged for the right hemisphere. The percent change in log-transformed mean-power of EEG within 0.5Hz-11.25Hz frequency band was computed for the first 10 sec of ON periods (i.e., the onset response [15] [19]) relative to the first 10 sec of OFF periods.

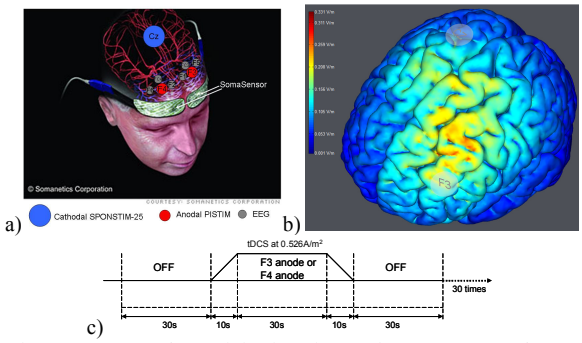


Fig. 1. NIRS-EEG/tDCS joint-imaging study. a) NIRS-EEG/tDCS joint-imaging montage, b) Electric field magnitude in the grey matter due to F3 cathodal and Cz anodal tDCS, c) study protocol

B. Corticospinal excitability changes to anodal tDCS

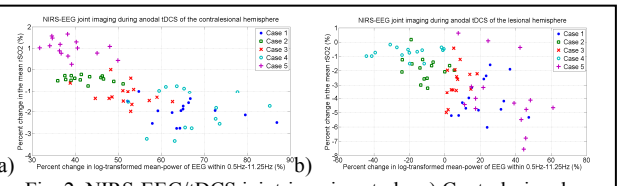
In a separate set of experiments (with more than a week interval) on the same five chronic (>6 months, see Table 1) ischemic stroke survivors, evaluation of corticospinal excitability changes to tDCS in the lesional and

contralesional hemisphere was conducted with single-pulse TMS-based motor evoked potentials (MEP) from resting first dorsal interosseous (FDI) muscle. Bilateral FDI muscle electromyogram (EMG) was recorded via Ag/AgCl electrodes where the raw signals were amplified, band-pass filtered at 1-200Hz and digitized at a sampling rate of 1000Hz for offline analysis in Matlab (The Mathworks, Inc., USA). The 'hotspot' for FDI was identified and marked as the position on scalp where most stable MEP amplitudes (comparable for at least 5 out of 10 trials) were elicited with the coil held 45° to the midline, tangentially to the skull and the handle pointing backwards (current flowing posterior-anterior). The TMS intensity was set during baseline measures of each session such that the MEP amplitude was about 1mV at the hot-spot for at least 5 out of 10 trials.

Table 1: Subjects (M: male, F: female, MCA: middle cerebral artery)

Case	Age/gender	Diagnosis	Year of stroke
1	68/M	Right MCA stroke	2010
2	74/F	Left MCA stroke	2011
3	76/M	Left MCA stroke	2011
4	72/M	Right MCA stroke	2012
5	75/M	Right MCA stroke	2012

PISTIM (Neuroelectrics, Spain) electrodes were placed over C3 (corresponding to the left M1 [22]) or C4 (corresponding to the right M1 [22]) of the international 10-20 EEG system, and two SPONSTIM-25 (Neuroelectrics, Spain) electrodes were placed over the supra-orbital region. For left M1 stimulation, C3 was anode and the contralateral supra-orbital electrode was cathode, whereas for right M1 stimulation, C4 was anode and the contralateral supra-orbital electrode was the cathode. The current was ramped up in 30 sec, maintained at 0.526A/m^2 for 15 min, and then ramped down in 30 sec for either the lesional or the contralesional hemisphere which were randomly ordered over two sessions with at least one-week gap between them for the wash-out. Before and immediately after the end of the 15min tDCS, eyes-open resting state EEG (StarStim, Neuroelectrics, Spain) was recorded at 500Hz from F3, F4, C3, Cz, C4, P3, P4 (international 10-20 system) for roughly 3 mins with CMS/DRL electrodes placed in the left mastoid. The raw EEG was pre-processed using EEGLAB functions [21] where artefactual epochs were also removed following subsequent visual inspection of the data. Then, the percent change in log-transformed mean-power of EEG within 0.5 Hz - 11.25 Hz frequency band was analyzed for both the lesional and contralesional hemispheres - F3, C3, P3 were averaged for left hemisphere and F4, C4, P4 were averaged for the right hemisphere. This average power spectrum was analyzed for 25 successive 4 sec artifact-free epochs (i.e., ~100 sec immediately before and ~100 sec immediately after tDCS) using Welch's averaged, modified periodogram spectral estimation method (MATLAB function "spectrum.welch") [23]. The changes in the cortico-spinal excitability were evaluated with 25 MEPs from resting FDI muscle with single-pulse TMS at the 'hotspot' before (Pre) and after (Post 0) the completion of the tDCS session as well as the EEG recordings (also, after removal of EEG-tDCS electrode cap so roughly 5min delay).



a) b)

Fig. 2. NIRS-EEG/tDCS joint-imaging study. a) Contralesional hemisphere, b) Lesional hemisphere

III. Results

A. NVC evaluation with NIRS-EEG/tDCS joint-imaging

There was an increase in log-transformed mean-power of EEG within 0.5 Hz-11.25 Hz frequency band in the first 10 sec of ON periods relative to the first 10 sec of OFF periods for the contralesional hemisphere stimulation/recording (see Figure 2). This increase was primarily in the Theta (4–8 Hz) frequency band in agreement to our prior results [15]. Also, there was a corresponding decrease in the mean rSO2 in the first 10 sec of ON periods (i.e., the onset response [15] [19]) relative to the first 10 sec of OFF periods (see Figure 2) where individual baseline for rSO2 measurements was set at the beginning of the session. Figure 2 shows that the percent change in the mean rSO2 mostly correlated with the corresponding percent change in log-transformed mean-power of EEG within 0.5 Hz-11.25 Hz frequency band during the onset response [15][19].

B. Corticospinal excitability changes to anodal tDCS

The percent change in the log-transformed mean-power of EEG (100sec EEG signal [23]) post-tDCS (Post 0) from baseline (Pre) within 0.5 Hz - 11.25 Hz frequency band for both lesional and contralesional hemispheres was variable across subjects (see Figure 3). Here, significant inter-subject variability was also found in the percent change in the MEP-measure of corticospinal excitability post-tDCS (Post 0) from the baseline (Pre) value. However, it was found that a post-tDCS decrease from baseline of log-transformed mean-power of EEG within 0.5 Hz - 11.25 Hz corresponded with a post-tDCS increase in the MEP-measure of corticospinal excitability from baseline, as shown in Figure 3.

IV. Discussion

In this paper, we presented results from two separate stroke studies - NIRS-EEG/tDCS joint-imaging study [19] and corticospinal excitability study - conducted on the same cohort of stroke survivors. We found across subjects that post-tDCS percent change in the mean rSO2 from baseline typically correlated with the respective post-tDCS percent change in the log-transformed mean-power of EEG within 0.5 Hz - 11.25 Hz frequency band (see Figure 2). In our prior work also [15], we found an immediate change in log-transformed mean-power of EEG in the 0.5

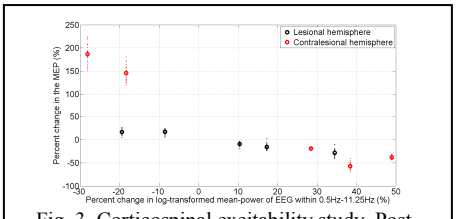


Fig. 3. Corticospinal excitability study. Post-tDCS changes in the MEP-measure of corticospinal excitability corresponded with the post-tDCS changes in the log-transformed mean-power of EEG from baseline.

Hz - 11.25 Hz frequency band during tDCS; however, there was also a significant inter-subject variability in this onset response [15][19]. In the corticospinal excitability study, post-tDCS decrease in the log-transformed mean-power of EEG within 0.5 Hz - 11.25 Hz corresponded with post-tDCS increase in the MEP-measure of corticospinal excitability across subjects (see Figure 3). Here, corticomuscular coherence may be a better correlate of the post-tDCS percent change in the MEP amplitude [24]. In both the studies, we investigated local post-tDCS changes from baseline at the site of anodal tDCS - F3/F4 in the NIRS-EEG/tDCS joint-imaging study and C3/C4 in the corticospinal excitability study, however, a significant limitation is due to the fact that these results are from two separate studies (although on same cohort). Another limitation is due to the differences in the tDCS electrode montage in these two studies. In our future studies, we will combine NIRS-EEG/tDCS joint-imaging with corticospinal excitability investigation. For example, innovative technologies for portable NIRS-EEG neuroimaging [25] can be leveraged to objectively guide and quantify the progress (e.g., corticospinal excitability alterations) of tDCS intervention as an adjuvant treatment during neurorehabilitation where system identification and parameter estimation techniques can be used to track corticospinal excitability alterations for closed-loop control of tDCS. Moreover, integrity of task-specific contralateral and ipsilateral pathways may be determined with NIRS-EEG neuroimaging and leveraged towards design of subject-specific electrode montages. Here, spatiotemporal NIRS-EEG brain activation patterns as a marker of underlying residual function that correlate with the functional outcome and/or performance may be facilitated with individualized brain-state dependent tDCS during neurorehabilitation [3].

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