33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Independent component analysis of resting brain activity reveals transient modulation of local cortical processing by transcranial direct current stimulation

Anusha Venkatakrishnan, José L. Contreras-Vidal*, Marco Sandrini, and Leonardo G. Cohen*,

Abstract— **Neuroplasticity induced by transcranial direct current stimulation (tDCS) contributes to motor learning although the underlying mechanisms are incompletely understood. Here, we investigated the effects of tDCS on resting brain dynamics recorded by whole-head magnetoencephalography (MEG) pre- and up to 35 minutes post-tDCS or sham over the left primary motor cortex (M1) in healthy adults. Owing to superior temporal and spatial resolution of MEG, we sought to apply a robust, blind and data-driven analytic approach such as independent component analysis (ICA) and statistical clustering to these data to investigate potential neuroplastic effects of tDCS during resting state conditions. We found decreased alpha and increased gamma band power that outlasted the real tDCS stimulation period in a fronto-parietal motor network relative to sham. However, this method could not find differences between anodal and cathodal polarities of tDCS. These results suggest that tDCS over M1 modulates resting brain dynamics in a fronto-parietal motor network (that includes the stimulated location), indicative of within-network enhanced localized cortical processing.**

I. INTRODUCTION

Noninvasive cortical stimulation techniques such as transcranial direct current stimulation (tDCS) have been widely used to modulate cortical excitability, particularly in the motor cortex, to promote plasticity and augment functional recovery along with functional rehabilitative techniques [1]. However, the mechanisms underlying neuroplastic changes induced by tDCS are poorly understood. One approach to gain insight into these mechanisms is the investigation of changes induced by tDCS on resting brain activity, which is known to show neuroplastic modulation after motor learning [2]. Recently, evidence of changes in resting brain activity immediately after tDCS has been shown in fMRI and EEG using connectivity-based model driven analysis [3], [4]. However, resting oscillatory dynamics post-tDCS were less differentiable relative to sham [4]. Thus, here we sought to use blind, data-driven analysis of whole-head brain activity as it may provide unbiased insights that advance the understanding of mechanisms affected by tDCS.

In this context, a method combining independent component analysis (ICA) and statistical clustering is a rigorous, blind approach that allows separation of surface summed cortical activity into underlying functional network function associated with specific spectral signatures. Tracking changes in these networks in terms of their spectral characteristics can be very useful to describe functional neural processes engaged/modified by a specific experimental intervention. Previously, this technique as applied to electroencephalographic (EEG) data recorded during performance of a visuomotor learning task was useful to identify and track changes across time in functional oscillatory networks associated with motor learning [5]. Here we applied this method to whole-head MEG activity to identify the temporal profile of changes induced in oscillatory network dynamics up to 35 minutes after tDCS.

II. METHODS

A. Experimental procedure and Data acquisiton

Twelve right-handed (6 females), neurologically healthy adults (23-40 yrs, mean age 27.2 $\pm$ 5.7 yrs) participated in this study after providing informed consent as approved by the Institutional Review Board (IRB) at the National Institute of Neurological Disorders and Stroke. Neuromagnetic data were recorded at 600 Hz with a bandwidth of 0-150 Hz using a CTF 275 MEG system (CTF Systems, Inc., Canada) composed of a whole-head array of 275 radial 1st order gradiometer/SQUID channels housed in a magnetically shielded room (Vacuumschmelze, Germany).

Manuscript received March 26, 2011. This work was supported by the Department of Defense in the Center for Neuroscience and Regenerative Medicine, Uniformed Services University of Health Sciences, Bethesda, MD USA and the Intramural Research Program of National Institute of Neurological Disorders and Stroke (NINDS), Bethesda, MD USA.

A. Venkatakrishnan is with the Graduate Program in Neuroscience and Cognitive Science, University of Maryland, College Park, MD 20742 USA, Human Cortical Physiology and Stroke Neurorehabilitation Section, NINDS, Bethesda, MD 20892 USA, and Center for Neuroscience and Regenerative Medicine at the Uniformed Services University of Health Sciences, Bethesda, MD 20814 USA (phone: 301-451-1932; fax: 301-402-7010; e-mail: venkatakrishna@ninds.nih.gov).

J. L. Contreras-Vidal is with the Department of Kinesiology, and the Graduate Programs in Bioengineering, and Neuroscience and Cognitive Science, University of Maryland, College Park, MD 20742 USA (e-mail: pepeum@umd.edu).

M. Sandrini is with the Human Cortical Physiology and Stroke Neurorehabilitation Section, NINDS, Bethesda, MD 20892 USA, and Center for Neuroscience and Regenerative Medicine at the Uniformed Services University of Health Sciences, Bethesda, MD 20814 USA (e-mail: sandrinim@ninds.nih.gov).

L. G. Cohen is with the Human Cortical Physiology and Stroke Neurorehabilitation Section, NINDS, Bethesda, MD 20892 USA (e-mail: cohenl@ninds.nih.gov).

* These authors contributed equally to this work.

Fig. 1. A) Experimental timeline. Pre and Post (Post-Immediate, Post-10, Post-20, and Post-30 min respectively) tDCS MEG blocks (5 min each) separated by 5 min intervals during which no data was recorded. B) Bipolar electrode montage for anodal tDCS application over left M1 is shown; red depicts the anode position over the M1 and black, the contralateral supraorbital cathode. Polarities were reversed for cathodal tDCS.

Synthetic 3rd gradient balancing was used to remove background noise on-line. Participants, blind to type of stimulation, participated in 3 sessions – anodal/cathodal/sham tDCS, at least 24 hours apart, with the order of stimulation pseudo-randomized and balanced. Target region for stimulation i.e., left M1 was determined by transcranial magnetic stimulation targeting the optimal scalp position to elicit motor evoked potentials of the right abductor pollicis brevis. A Phoresor II Auto (model PM850, IOMED, Salt Lake City, UT) device was used to apply tDCS over M1 using a bipolar montage with the cephalic reference electrode over the right supraorbital area. The DC stimulation was delivered by 25 cm^2 conducting electrodes covered by saline-soaked sponge, at an intensity of 1 mA (DC current density 0.04 mA/cm^2; total charge 0.048 C/cm^2) for 20 min in the anodal and cathodal tDCS sessions and for up to 20 seconds in the sham session according to a previously described method [6]. Rest MEG recordings were performed in 5 blocks of 5 minutes each (see fig. 1), 1 before (Pre) and 4 after stimulation, allowing measurement of changes up to 35 minutes post-tDCS. During the recording, participants were instructed to stay completely still and relaxed with their eyes closed. Additionally, in order to maintain same head-MEG sensor array configuration, head position with respect to sensor array was recorded each time, and adjusted to maintain constant position with a tolerance of 0.5 cm. Subjects were also provided with a chin strap to prevent motion of the head during recording.

B. Data Pre-processing

Data from each rest block (3 min, excluding the first and last minute of recording) per subject were demeaned and band-pass filtered between 0.15-150 Hz using a 4^{th} order, zero-phase, Butterworth filter and notch-filtered at 60 and 120 Hz using a 2^{nd} order Chebyshev-type1 filter to remove line noise.

C. Independent Component Analysis and Clustering

Each rest block of data was subjected to an extended Infomax independent component analysis (ICA) to decompose it into spatially overlapping, temporally independent components. All analyses were performed using custom written programs employing the EEGLAB toolbox[7] in MATLAB 7.11 (The Mathworks, Inc, Natwick, MA).

Component clustering was performed in 3 consecutive steps. *Step 1*: K-means clustering algorithm was used to identify and partition consistent patterns of activation across subjects within each block for each stimulation condition. The algorithm was iteratively optimized to extract K mutually exclusive clusters by minimizing the sum of squared Euclidean distances of each object in the cluster from its centroid. Features used for clustering include (1) scalp component map (2) power in functional rhythms (delta:1-4 Hz, theta: 4-8 Hz, alpha: 8-13 Hz, beta: 13-30 Hz, low gamma: 30-50 Hz, high gamma: 70-100 Hz) computed by integrating power spectral density (PSD) obtained using multitaper method, between frequency intervals (3) component kurtosis and (4) component entropy (281 features total). The use of spectral as well as topographic features in combination for clustering allowed identification of cortical networks with similar spatiotemporal characteristics. Clusters with artifacts were identified by visual inspection of cluster mean scalp map and kurtosis values and were excluded from further analyses. *Step 2*: In order to link changing clusters across blocks (Pre, Post-Imm, Post-10, Post-20, Post-30) to characterize temporal profile of effects of tDCS on brain dynamics, K-means centroids from step 1 were hierarchical clustered based on Euclidean distance inconsistencies (thresholded at 0.9). Cophenetic correlation coefficients were further computed between clustering decision and data structure to assess the quality of classification suggested by clustering. *Step 3*: This step was performed to test the null hypothesis that no differences existed between the 3 stimulation conditions. Clusters identified from step 2 for each stimulation condition were subjected to hierarchical clustering (as in step 2), first within each block, and next across blocks. If differences existed between the 3 tDCS conditions, then networks identified within each stimulation condition would cluster separately at this step. Cophenetic correlation coefficients were computed similar to Step 2. Finally, spectral characteristics of identified clusters (representative of networks) between different blocks were compared directly based on 95% confidence intervals generated based on bootstrapped distributions (n=100000) of mean power in each frequency band.

III. RESULTS

The blind ICA decomposition and clustering method identified 3-5 functional clusters for each stimulation condition at all times of measurement, retaining over 90% of artifact-free data. Cophenetic coefficients computed for both steps of hierarchical clustering were greater than 0.9

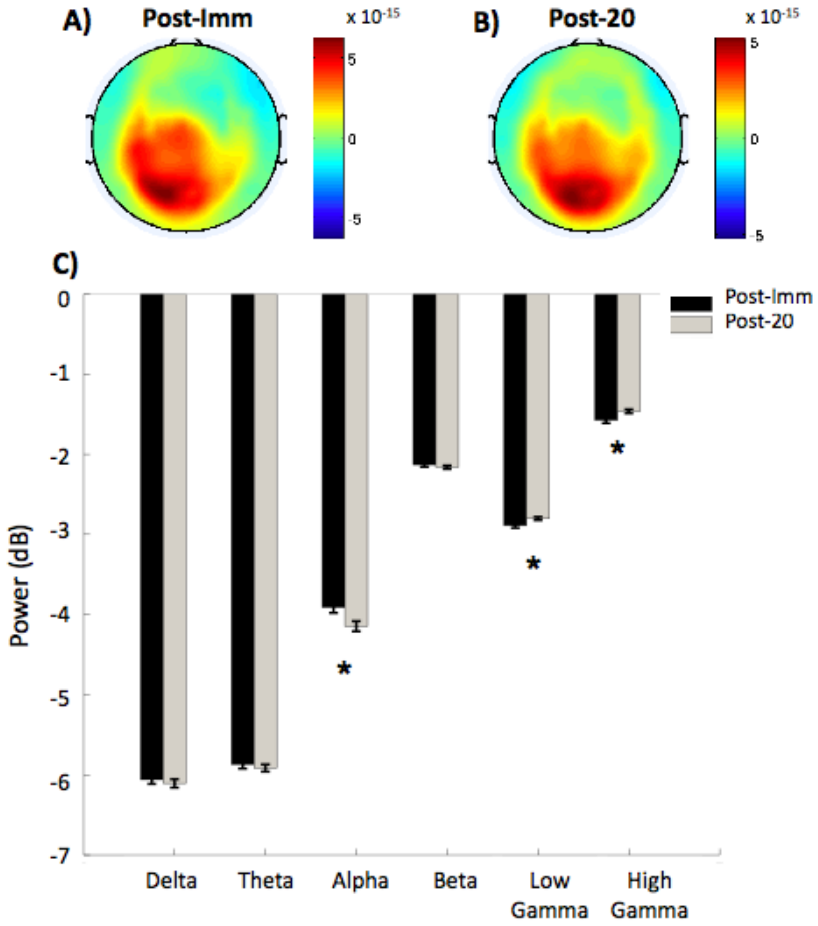

Fig. 2. Real tDCS engaged a parieto-motor network (A) immediately and (B) 20 minutes after stimulation respectively. (Topoplots of cluster means are shown, with activation in femtotesla.) (C) The spectral signature of this network showed a progressive decrease in alpha power and increase in low and high gamma power. Error bars represent 95% confidence intervals. Significant differences in power are indicated by * ($p < 0.05$).

indicating correct clustering. All 3 stimulation conditions were represented across 4 functional networks identified pre-tDCS by step 3 clustering.

However, this method identified an effect of real tDCS relative to sham in a left parieto-motor network characterized by a progressive decrease in alpha and increase in gamma band power, starting immediately and lasting up to the Post-20 block after stimulation (Fig. 2). This network appeared only following tDCS in Post-Imm and also transiently engaged frontal regions in the Post-10 block after tDCS (Fig. 3). Using this approach, no differences between anodal and cathodal tDCS were found. No differences between real tDCS and sham were identifiable in the last block i.e., Post-30 minutes following stimulation.

IV. DISCUSSION

The temporal profile of neuroplastic changes in large-scale oscillatory network dynamics induced by tDCS is presently unknown. Here, we show that real tDCS over M1 produces changes in resting cortical dynamics in a related parieto-motor network indicative of within-network enhanced local cortical processing. Importantly, we show that these network changes are persistent for up to 25 min post-tDCS. These findings are important in advancing our understanding of the mechanisms mediating lasting effects of non-invasive cortical stimulation over M1 and its influence over a distributed fronto-parietal motor network.

A. General Considerations

We demonstrate for the first time the feasibility of using a data-driven method combining ICA and statistical clustering to study neuroplastic changes in cortical network dynamics affected by tDCS, both in terms of altered regional activity and cortical dynamics. The identified network here comprises neural regions that are functionally and structurally interconnected and relevant to motor control and learning. Surprisingly, our method failed to find differences between anodal and cathodal polarities of tDCS. Several factors could account for absence of polarity-specific effects. Since anodal and cathodal polarities of stimulation are directed over the same, relatively large cortical area (M1), cortical activity detected by MEG, within folds in

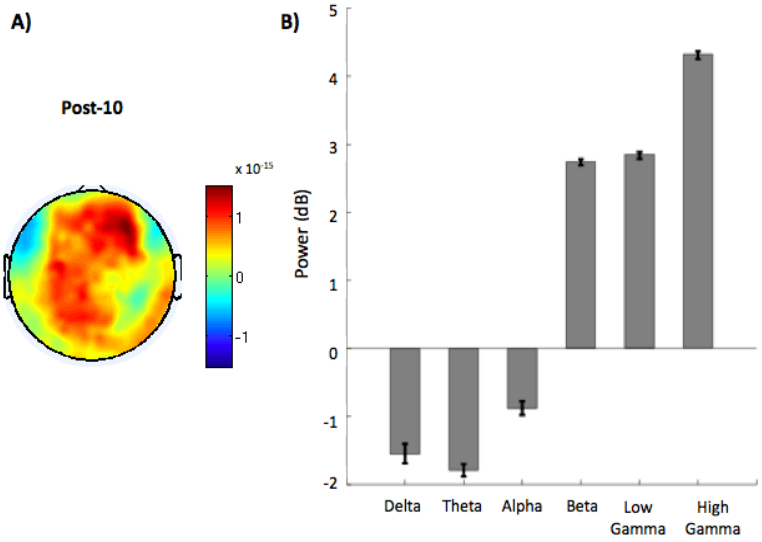

Fig. 3. A) Real tDCS also caused the parieto-motor network to transiently engage frontal cortical regions. This network was hierarchically clustered different from the parieto-motor network in fig. 2 due to different topology. B) The spectral signature of this network is also characterized by higher power in higher frequencies, namely, beta, low, and high gamma. Error bars represent 95% confidence intervals.

underlying cortical gyri, may be insensitive (i.e., cancel out) to subtle differences in polarity-specific activation of underlying neural populations. Indeed, the lack of difference in cortical oscillatory dynamics observed here is consistent with evidence from magnetic resonance spectroscopy showing localized reduction in γ-amino-butyric acid i.e., GABA following both anodal and cathodal tDCS [8]. Similarly, increases in PET (positron emission tomography) regional cerebral blood flow in frontal and sensorimotor cortical regions have not shown polarity-specific differences after tDCS relative to sham [9]. Alternatively, this data analytical approach may be insensitive to subtle differences in cortical network dynamics caused by anodal versus cathodal tDCS. Thus, work is underway to analyze these network dynamics in anatomical source space to disentangle polarity-specific effects of tDCS.

B. Clinical Implications

tDCS is rapidly gaining popularity as an adjunct for neurorehabilitation of motor and cognitive impairments [10-13]. Thus, clearer understanding of functional changes induced in specific networks engaged by tDCS could lead to a more principled application of this technique. If network changes as identified here are shown to parallel behavioral improvements induced by tDCS, it is conceivable that in the future, individual analysis of the changes in cortical dynamics induced by tDCS could predict the magnitude of behavioral effects, an issue of potential clinical relevance. Such neural biomarkers could contribute to effective rehabilitation strategies by allowing direct monitoring of patient response to treatment.

V. CONCLUSION

In summary, these results document a strong effect of motor cortical tDCS in enhancing local cortical processing in a specific fronto-parietal motor network. This finding has implications for the understanding of mechanisms underlying tDCS effects on cortical function and for optimizing its use to augment neuroplasticity in patients with brain lesions like traumatic brain injury (TBI) and stroke for neurorehabilitation.

ACKNOWLEDGMENT

This study utilized the high-performance computational capabilities of the Biowulf PC/Linux cluster at the National Institutes of Health, Bethesda, MD. A. Venkatakrishnan thanks Tom Holroyd and Fred Carver from the MEG core facility at the National Institute of Mental Health, Bethesda, MD for their assistance.

REFERENCES

[1] M. Nitsche et al., "Transcranial direct current stimulation: State of the art 2008," Brain Stimulation, vol. 1, no. 3, p. 206-223, 2008.

[2] N. B. Albert, E. M. Robertson, and R. C. Miall, "The resting human brain and motor learning," Current biology : CB, vol. 19, no. 12, p. 1023-1027, Jun. 2009.

[3] R. Polanía, W. Paulus, A. Antal, and M. A. Nitsche, "Introducing graph theory to track for neuroplastic alterations in the resting human brain: A transcranial direct current stimulation study," NeuroImage, Oct. 2010.

[4] R. Polanía, M. A. Nitsche, and W. Paulus, "Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation," Human Brain Mapping, Jul. 2010.

[5] J. L. Contreras-Vidal and S. E. Kerick, "Independent component analysis of dynamic brain responses during visuomotor adaptation.," NeuroImage, vol. 21, no. 3, p. 936-945, Mar. 2004.

[6] P. C. Gandiga, F. C. Hummel, and L. G. Cohen, "Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation.," Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, vol. 117, no. 4, p. 845-850, Apr. 2006.

[7] A. Delorme and S. Makeig, "EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis," Journal of neuroscience methods, vol. 134, no. 1, p. 9-21, Mar. 2004.

[8] C. J. Stagg et al., "Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation.," The Journal of neuroscience : the official journal of the Society for Neuroscience, vol. 29, no. 16, p. 5202-5206, Apr. 2009.

[9] N. Lang et al., "How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain?," The European journal of neuroscience, vol. 22, no. 2, p. 495-504, Jul. 2005.

[10] F. C. Hummel, K. Heise, P. Celnik, A. Floel, C. Gerloff, and L. G. Cohen, "Facilitating skilled right hand motor function in older subjects by anodal polarization over the left primary motor cortex.," Neurobiology of aging, vol. 31, no. 12, p. 2160-2168, Dec. 2010.

[11] A. Floel and L. G. Cohen, "Recovery of function in humans: cortical stimulation and pharmacological treatments after stroke.," Neurobiology of disease, vol. 37, no. 2, p. 243-251, Feb. 2010.

[12] C. Miniussi et al., "Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation.," Brain Stimulation, vol. 1, no. 4, p. 326-336, Oct. 2008.

[13] R. Sparing, M. Thimm, M. D. Hesse, J. Küst, H. Karbe, and G. R. Fink, "Bidirectional alterations of interhemispheric parietal balance by non-invasive cortical stimulation," Brain, vol. 132, no. 11, p. 3011-3020, Nov. 2009.