

## Resting-State Functional Connectivity Modification by Non-invasive Electrical Stimulation of the Brain

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**Introduction:** Recent advancements in non-invasive electrical stimulation of the brain (ESB) have provided simple and minimal risk options to undo some deficits in neural communication within the central nervous system. Furthermore, using either direct current stimulation (tDCS) or pulsed current stimulation (tPCS) appears to enhance CNS connectivity.<sup>1</sup> Favorable clinical outcomes have been reported for patients with Parkinson's Disease<sup>2-4</sup>, stroke<sup>5,6</sup>, clinical depression<sup>7,8</sup>, and chronic pain<sup>9</sup>. The modes of action leading to the reported clinical results are still in the exploratory phase<sup>10</sup>. Given the favorable clinical outcomes in these studies we hypothesize that the resting state networks may be altered following direct electrical stimulation of the brain. In this study we report the changes in resting state motor network following electrical stimulation of the motor cortex using both tDCS and tPCS.

**Methods:** Five subjects participated in two separate MRI sessions separated by one week. In each session, subjects were fitted with a thin thermoplastic molded cup that included two 7cm x 4.5 cm (area 31.5 cm<sup>2</sup>) carbon-silicon flexible electrodes. The positive electrode was positioned over the right primary motor area of the cortex (M1) and the negative electrode over the supra-orbital area on the left side of the head. Electric stimulation was provided by a transcranial stimulator (Fisher Wallace, New York). Imaging was performed on a Siemens 3T Tim Trio scanner with a 12-channel head coil. Functional images were acquired using single-shot EPI T2\*-sensitive sequence (TE = 30 ms, TR = 3s, 1.8 x 1.8 mm<sup>2</sup> in-plane resolution and a FOV of 23 cm) using 36 axial slices (4 mm thick) with no gap between slices for a total acquisition time of 6:27. A T1-weighted MPAGE image (TE = 3.44ms, TR = 2s, TI = 900ms, flip angle = 9°, 72 slices, slice thickness 2 mm, 0.898 x 0.898 mm<sup>2</sup> in-plane resolution and a FOV of 23 cm) was acquired for anatomic reference. Following the acquisition of anatomical data, five separate functional scans were obtained from the subjects. The first scan consisted of a resting state scan with no electrical stimulation. The second scan consisted of a motor paradigm that involved a self-paced finger-thumb opposition task using a block design with 20s-On and 20s-Off for a total of 8 cycles. The third scan consisted of a resting state scan with continuous tDCS applied. The fourth scan consisted of a resting state scan with no electrical stimulation, which was followed by the final scan which consisted of a resting state scan with continuous tDCS applied. The tDCS current intensity used was 2 mA. The exact procedures were repeated during their second visit, one week later, where tPCS at 1 mA intensity (peak current of 4 mA) was applied instead of tDCS. For all resting state scans, subjects were instructed to close their eyes and try not to fall asleep.

Data were analyzed using AFNI and MATLAB. Preprocessing of the functional time series data included slice-timing correction, motion correction, 6mm FWHM Gaussian blurring, and normalization to percent signal change. The MP-RAGE data was registered to the base functional time series for anatomical reference. For the fMRI motor scan, a general linear model was used to determine the voxels' correlation with the motor task paradigm. Based on the activation maps from the motor paradigm, a mask containing the most active cluster of voxels centered on the right motor area (RM) was created, and spherical ROIs centered on the RM and left motor area (LM) were chosen. The time courses of the voxels within the cluster mask were averaged and used as a regressor in the GLM analysis of the resting state data to produce motor area resting state network (MARSN) images. The mean correlation coefficients in the spherical regions centered on the RM and LM were then compared between the electrically stimulated resting state (tDCS or tPCS) and the non-stimulated resting state.

### Results:

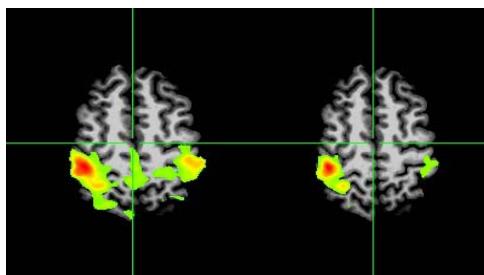


Figure 1- Representative Motor Area Resting State Network (MARSN)  $R^2$  maps for no stimulation(L) versus tPCS(R), thresholded at  $p<1e-5$ , showing reduced functional connectivity between LM and RM during tPCS stimulation.

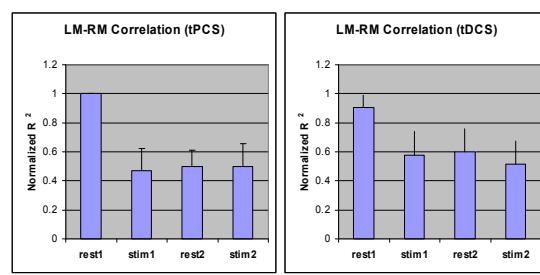


Figure 2 – LM↔RM MARSN  $R^2$  correlations averaged for 5 subjects showing reduced functional connectivity during and after the first stimulated resting state scan (stim1) for tPCS and tDCS.

The electrical stimulation devices did not produce any additional noticeable noise. In the case of the tPCS, the correlation coefficient between the LM and RM decreased during the tPCS scan (Figs 1, 2). The effects of this stimulation appear to last for at least 6-7 minutes as the correlation coefficients remained suppressed during the second non-stimulated resting state scan. There seems to be no further effect from repeated stimulation. While we saw decreased correlation coefficients with tDCS between the LM and RM as well, the effects were not as pronounced and there was more inter-subject variability than with tPCS.

**Conclusion:** Our study demonstrates that electric current stimulation, either direct or pulsed, can be safely applied within a 3T magnet without any data degradation. Further, our study indicates that (a) electrical stimulation affects the resting state networks, (b) stimulation effects are persistent, and (c) the effect on the resting state is dependent on the type of electrical stimulation provided (tDCS or tPCS). We are unaware of studies that have looked at the CNS effects from electrical stimulation directly in the brain, but our preliminary results suggest that functional connectivity MRI studies can help elucidate the mechanisms responsible for therapeutic effects of electric stimulation.

### References :

[1]Bolognini N et al., J Neuroeng Rehabil 2009, 6:8 [2]Wu AD et al. Neurotherapeutics 2008, 5(2):345-361. [3]Fregni F et al, Mov Disord 2006, 21(10):1693-1702. [4] Boggio PS et al. J Neurol Sci 2006, 249(1):31-38. [5] Celnik P et al., Stroke 2009, 40(5):1764-1771. [6]Hummel F et al., Brain 2005, 128(Pt 3):490-499. [7] Ferrucci R et al., J Affect Disord 2009, 118(1-3):215-219. [8]Gabis L et al., J Rehabil Med 2009, 41(4):256-261. [9]Mori F et al., J Pain, 11(5):436-442. [10]Polania R et al., Hum Brain Mapp.