

# Modulation of Resting State Functional Connectivity of the Motor Network by Transcranial Pulsed Current Stimulation (tPCS)

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**Purpose:** Non-invasive electrical stimulation of the brain (ESB) is able to alter cortical excitability. The therapeutic potential of non-invasive ESB is being actively explored by many groups, but an ongoing debate regarding the physiological basis of these electrical modulators continues. Two broad classes of stimulators use either a direct current (referred to as tDCS) or a pulsed current (referred to as tPCS). Previous work investigating modulation of cortical activity using resting state functional connectivity (rs-FC) has focused on cortical alterations induced by tDCS<sup>1-3</sup>. We aim to expand upon previous results investigating tDCS by exploring the effects of unilateral anodal tPCS applied over the right primary motor cortex on rs-FC within the motor network both during stimulation and directly after stimulation.

**Methods:** Eleven healthy volunteers participated in this study (age: 29.8yrs  $\pm$  9.1; 6 male: 5 female). Custom made MRI compatible cap and electrodes were used during stimulation. The electrodes were positioned on the scalp with the positive electrode (anode) over the right primary motor cortex (M1) and the negative electrode (cathode) over the left supra-orbital area. The tPCS stimulator (Fisher Wallace model FW 100Ctm, New York, NY) delivered a monophasic waveform with a pulse duration of 33.3  $\mu$ s and an interpulse interval of 33.3  $\mu$ s with a carrier frequency of 15kHz with stimulation lasting on average of 13 minutes.

A high resolution T1-weighted-MPRAGE (TE = 3.44 ms, TR = 2250ms, TI = 900ms, flip angle = 9°, resolution = 256  $\times$  256  $\times$  96, FOV = 22 cm, sl. Thick. = 1.5 mm) was acquired for anatomic reference. The functional MRI scans were acquired with T2\*-weighted imaging using a single-shot EPI sequence (TE = 30 ms, TR = 3000 ms, FOV = 230 mm, resolution = 64  $\times$  64) with 36 axial slices (sl. thick. = 4 mm). Total acquisition time of 6 minutes and 24 sec. Four fMRI scans were acquired, one motor paradigm consisting of bilateral finger tapping task (block design: 24 seconds finger tapping/24 seconds rest), and three (PRE-STIM, during STIM, POST-STIM) resting state fMRI scans.

The motor fMRI was analyzed using FSL to extract activation patterns during the bilateral finger-tapping paradigm. Rs-FC processing was performed using the CONN-fMRI Functional Connectivity toolbox v13.h<sup>4</sup>. Seed based method of analysis using seed regions selected based on the group activation patterns from the motor paradigm to create group rs-FC maps. 4X4 connectivity matrices were created by computing the Pearson's correlation between the time series from which we calculated two bivariate measures of rs-FC. The strength of node  $i$  is defined as the mean of  $i^{\text{th}}$  column of the connectivity matrix while the diversity of node  $i$  is defined as the variance of the  $i^{\text{th}}$  column<sup>5</sup>.

**Results and Discussion:** The motor paradigm resulted in activations in the right and left primary motor (R M1 and L M1), supplemental motor area (SMA), and cerebellum. Contrasts between group rs-FC maps demonstrate that compared to the PRE-STIM, during STIM there is reduced rs-FC with the L M1 and regions surrounding the L M1, but increased rs-FC with the left thalamus (Fig. 1AB). During the POST-STIM condition, contrasts between group rs-FC maps demonstrate that compared to the PRE-STIM, there is increased rs-FC between the cerebellum (Cer) and the right posterior insula (Fig. 1C).

4x4 correlations matrices shown in Fig. 2 demonstrate reduced rs-FC between the R M1 and L M1 during the STIM and POST-STIM conditions. Based on ROI analysis, bivariate rs-FC results based on the ROI analysis indicate that the average network strength was reduced during STIM compared to PRE-STIM ( $p=0.044$ ). Likewise, both the right and left M1 show reduced strength during STIM compared to the PRE-STIM condition ( $p=0.048$ ,  $p=0.042$ ) respectively. The strength of the network appears to normalize to baseline by the POST-STIM condition (Fig. 3A). The average network diversity is significantly reduced during STIM ( $p=0.024$ ). A trend of reduced diversity during STIM is observed in the right and left M1 compared to the PRE-STIM condition ( $p=0.10$ ,  $p=0.068$  respectively). During the POST-STIM condition, there was a trend towards reduced diversity for the average network ( $p=0.071$ ), R M1 ( $p=0.090$ ) and L M1 ( $p=0.058$ ) (Fig. 3B).

**Conclusion:** tPCS modulated the functional characteristics of the motor network during stimulation after the stimulation is stopped including reduced diversity. Reduced diversity may indicate that tPCS assists in the recruitment of maximum number of neurons that may be available to facilitate rehabilitation. While these data confirm previous findings by other investigators using tDCS, we also demonstrated changes in connectivity patterns that are specific to tPCS including thalamo-cortical and cerebellar-cortical involvement. Our data strengthen the evidence for the neuro-modulatory effects of tPCS. Future work is needed to directly link altered neuronal excitability to changes in behavior with the anticipated goal of transitioning tPCS into a clinical setting.

**References:** <sup>1</sup>Polania et al 2012. PLoS One. <sup>2</sup>Sehm et al. J Neurophysiol. 2012. <sup>3</sup>Sehm et al. Front Hum Neurosci. 2013. <sup>4</sup>Whitfield-Gabrieli et al., Brain Connect. 2012. <sup>5</sup>Lynall ME, et al., J Neurosci. 2010.

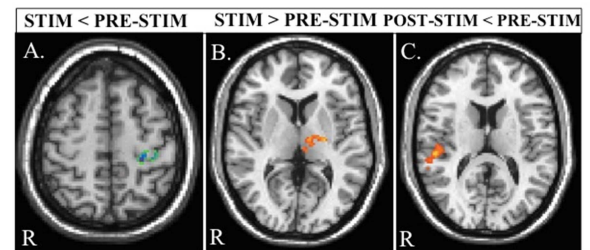


Figure 1: (A-B) L M1. (C) Cer. Maps were thresholded at voxel-wise  $p$ -value of 0.005 (unc) and cluster extent threshold of  $p$ -value of 0.05 (FEW). Cool colors represent reduced rs-FC, warm colors represent increased rs-FC.

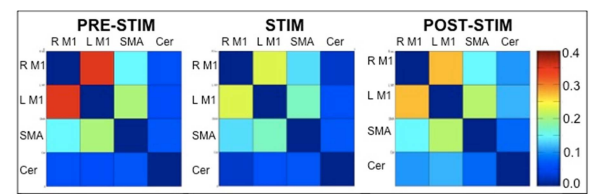


Figure 2: 4X4 Connectivity matrices for PRE-STIM, STIM and POST-STIM

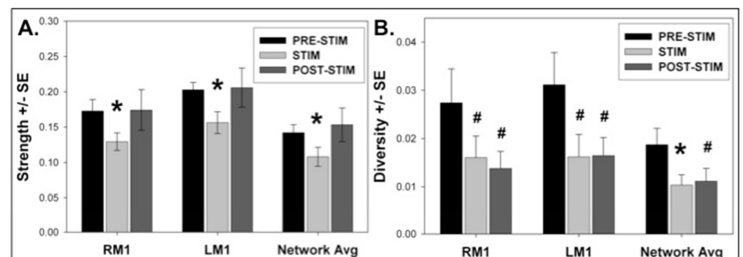


Figure 3: Bivariate connectivity measures (A) Strength and (B) Diversity for R M1, L M1 and network average. \*  $p < 0.05$  and #  $p < 0.10$  compared to baseline PRE-STIM condition.