In-vivo Evidence of transcranial Direct Current Stimulation (tDCS) induced magnetic-field changes in Human Brain revealed by MRI

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Target Audience: Neuroimaging scientists and clinicians interested in tDCS

Purpose: Transcranial Direct Current Stimulation (tDCS) is a non-invasive neuromodulation technique hypothesized to modulate cortical excitability. Through the application of a small current (~mA) using scalp electrodes, tDCS has been found to help with stroke recovery [1], depression [2] and pain relief [3]. Consequently, to improve tDCS's efficacy, there is an urgent need to identify the affected areas for a particular tDCS montage. To date, only simulation data or surrogate markers (BOLD, CBF) have provided measures of target engagement. The aim of this study was to develop a technique to image the "true" marker of tDCS (i.e. electrical current) using concurrent tDCS-MRI.

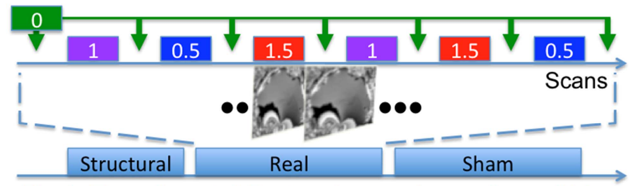

Fig 1. Experimental Protocol: pseudo-random within Session, Counterbalanced Sessions across subjects

Theory and Methods: Ampere's law states that an applied direct current induces a magnetic field that is proportional to the current. We used field-mapping MRI concurrently with applied tDCS to measure the component of the induced field aligned with the main magnetic field as phase.
Twelve healthy subjects (7M/5F) participated in a concurrent tDCS/MRI study on a Siemens 3T Trio scanner with a quadrature volume coil. Subjects were asked to stay awake and fixate on a cross during the scan.
tDCS: Two gel-wetted sponge electrodes (5 x 10cm) were secured bilaterally over the motor cortex. Electrical current was applied in 2 sessions of Real/Sham conditions (single blinded). Each session consisted of blocks with 0.5/1/1.5mA currents applied in a pseudo-randomized counterbalanced fashion, with interleaved 0mA blocks (Fig 1). The order of the Real/Sham sessions was counterbalanced across subjects. For Sham, the current was ramped up and maintained for 20 sec, then switched off.
MRI: Phase data was acquired for each current (including 0mA) using a field mapping sequence (TE1/TE2=4.92/14.76 msec, TR=1.15 sec, FA = 25^0, 65 slices, $2x2x3mm^3$ voxel, matrix: 128 x128, BW=750 Hz/pix,). An MPRAGE structural scan was also acquired.
Pre-processing: Phase data was unwrapped using the Region-Growing unwrap algorithm implemented in Phase Tools [4]. Using corresponding magnitude images, unwrapped phase data were coregistered to the first volume and smoothed with a $6x6x3mm^3$ Gaussian kernel.
First Level Analysis: The measured phase (Φ_{Meas}) can be expressed as [5]:
$\Phi_{Meas} = \Phi_0 + \Phi_{Current} + \Phi_{Non\text{-}Current} + \Phi_{Drift} + \Phi_{Motion} + \Phi_{Noise}$.
Exploiting the linear relationship between applied current and induced field (phase), Pearson correlation was chosen to compare applied current and $\Phi_{Current}$. $\Phi_{Current}$ was estimated as follows:

a) Φ_0 eliminated by using Phase gained in ΔTE
b) $\Phi_{Non\text{-}Current}$ is a level-shift (No correction needed)
c) Φ_{Motion} was modeled as a regressor using RMS-motion-between-scans
d) Φ_{Drift}, modeled as a regressor, was found to be the largest confound. It was estimated by fitting a Least Squares polynomial to the interleaved 0mA scans. The degree of the polynomial was adapted to make the residuals match the noise statistics (Gaussian) of the voxel (which are estimated independently [6]).

Second Level Analysis:
Subject Pearson-correlation maps were coregistered to their structural scans and then normalized to MNI space. We hypothesized that the largest detectable effect would be present beneath the electrodes (consistent with simulations). We used a 1-sample 2-sided t-test to compare the distribution of Pearson-correlations against 0 for each of the Real and Sham sessions, respectively.

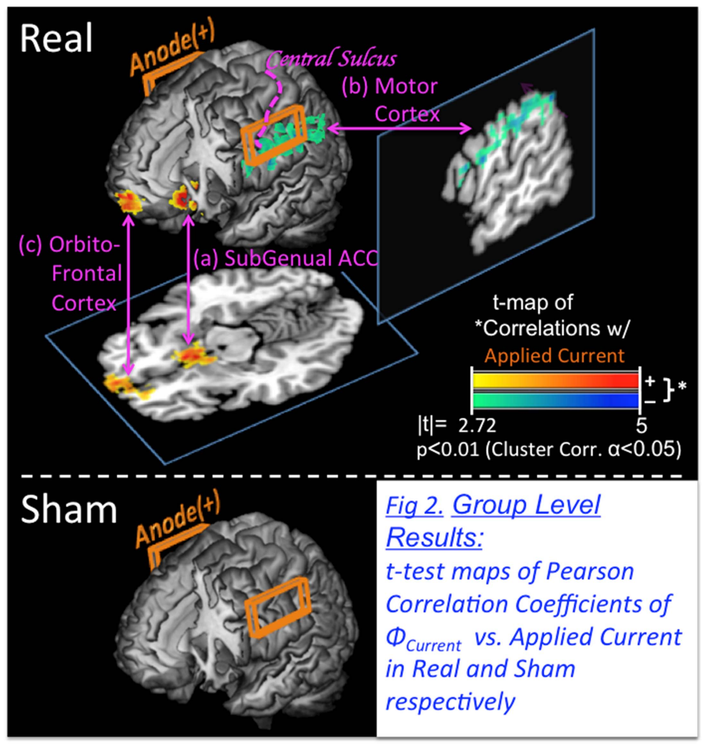

Fig 2. Group Level Results: t-test maps of Pearson Correlation Coefficients of $\Phi_{Current}$ vs. Applied Current in Real and Sham respectively

Results: The t-tests' results were thresholded to $p < 0.01$ and Cluster-corrected ($\alpha < 0.05$) to account for multiple-comparisons (Fig 2). No significant effects were observed beneath the electrodes for the Sham condition. In contrast, a significant group effect was observed beneath the Cathode (–). Additional group effects were observed in the subgenual Anterior Cingulate Cortex (ACC) and orbitofrontal areas. Group effects in Sham were only observed in the occipital and posterior parietal lobe.

Discussion and Conclusion: Our results provide imaging evidence that, group-wise, there is a *linear* phase change with applied current in the motor cortex, subgenual ACC and orbitofrontal areas. Coupled with the theoretical prediction of the same linear relationship between current and phase (Ampere's Law), this strongly suggests that the detected brain regions using phase mapping reflect true in-vivo electrical current effects of tDCS. Notably, the effects are both cortical and deep-brain. If true, this gives us concrete measures to evaluate tDCS montages vs. more invasive clinical techniques (e.g. Deep Brain Stimulation) within the framework of areas targeted in a clinical population (e.g. depression).
Currently, we are still investigating the group effects observed in the Sham block. A caveat of the Sham is that the current is still applied for a short duration (20s), which could be a possible cause of "Placebo" effect.

References: [1] Fregni F, et. al., Neuroreport. 2005; 16(14):1551-5 [2] Fregni F, et. al., Bipolar Disord. 2006; 8(2):203-4 [3] Fregni F, et. al., Pain. 2006;122(1-2):197-209. Epub 2006 Mar 27 [4] Barnhill E., et. al., Physiol. Meas. 2013; 34; 1675-98 [5] Jog M, et. al., ISMRM 2014, Prog# 0005 [6] Gudbjartsson H., et. al., MRM 1995; 34(6); 910-4