SUPPLEMENTARY MATERIAL

Leaver et al., Modulation of Brain Networks during MR-Compatible Transcranial Direct Current Stimulation

Supplemental Methods

Description of Study Volunteers. This study included data from three tDCS-fMRI cohorts using three different montages targeting DLPFC, LTA, or STC, which were combined here to increase sample size and potentially boost statistical power. These cohorts included patients with major depressive disorder (MDD), chronic tinnitus, and demographically matched controls. Volunteers with MDD reported having a diagnosis at least one year prior to participating in the study with mild-to-moderate symptoms. Volunteers with chronic tinnitus (a ringing or buzzing in the ear) reported experiencing symptoms for at least one year, which had been evaluated by a clinician and had no known medical cause (i.e., not caused by Meniere's Disease, acoustic neuroma, etc.). Some volunteers reported having both an MDD diagnosis and chronic tinnitus.

The following is a description of the number of volunteers in each tDCS cohort meeting criteria for MDD and/or chronic tinnitus: Seventeen of the 37 volunteers in the DLPFC-tDCS cohort reported having MDD, and 2 of these MDD patients also reported having chronic tinnitus. Seven of the 16 volunteers in the LTA-tDCS cohort reported having chronic tinnitus; 3 of these tinnitus patients also reported having an MDD diagnosis. All 11 volunteers in the STC-tDCS cohort had chronic tinnitus; two of these also endorsed having MDD. Mood disorder is common in chronic tinnitus [1], and so this heterogeneity is expected.

It is important to note that although this heterogeneity may have prevented us from detecting effects of tDCS (e.g., if functional connectivity in depressed patients was not affected by active DLFPC-tDCS), all critical statistical comparisons were applied within subjects, and thus this heterogeneity in patient status was unlikely to introduce spurious effects. Large-scale, independent validation of these results with balanced samples is certainly needed, however.

Stimulus Presentation. During MRI, every volunteer received 5 minutes each of active tDCS and sham tDCS in a randomized and counterbalanced order, initiated manually by the experimenter and timed with each scan (Supplementary Figure 1). During DLPFC-tDCS & LTA-tDCS, BOLD-fMRI scans began with 5 min Rest (no stim) followed by 5 min of either active or sham tDCS. This was followed by 5 min rest to create a 15 min duration scan at UCLA; NU scans were 10 min in duration (shortened to reduce volunteer burden). During STC-tDCS, each BOLD-fMRI scan was 5 min in duration, and the rest (no stim) scan occurred first, followed by either active or sham tDCS scans in randomized and counterbalanced order. For every volunteer, a T1-weighted anatomical scan was acquired between active tDCS and sham tDCS to serve as a "wash-out" period to avoid contamination (i.e., of sham tDCS by active tDCS), providing 10-15 minutes between stimulation conditions. This should provide adequate wash-out time [2], [3]; however, note that counterbalancing the order of active and sham conditions also mitigates the potential residual effects of active stimulation on the sham condition (i.e., when active tDCS is presented first). For details regarding impedance measurements (and associated current delivered) during sham and rest (i.e., device on) conditions, we refer the reader to the manufacturers of the respective devices, and note that direct comparison of sham conditions was not a goal of the current study.

RF Filters for tDCS Devices. In MR-compatible tDCS, the stimulation device is located outside the MRI scanner room, and MR-compatible cables are passed into the MRI scanner room via a shielded penetration panel. To minimize transmission of radio frequency (RF) noise to the scanning environment and subsequent effects on MR images, RF filters were included on these cables per manufacturer specifications and instructions for the neuroConn (neurocaregroup.com) and Soterix devices (soterixmedical.com) used at UCLA and NU, respectively. The NeuroConn DC-STIMULATOR PLUS MR device connects to a filter box ("OUTER BOX"), which filters RF noise ~50-140 MHz, placed as close as possible to the waveguide (i.e., pass-through) on the penetration panel and wrapped with aluminum foil sheets. From this filter box, an optical cable connected to a second box ("INNER BOX") located in the scanner bore, which connected to MR compatible electrode cables with 5 kOhm resistor on each wire. The Soterix device (1x1 tES Stimulator and 4x1-C3A HD-tDCS Multichannel Device) was connected to an RF filter installed in the penetration panel, which connected to an MRI-compatible coaxial cable (and finally electrode cables with 5.6 kOhm resistor on each wire. For both devices, connecting cables were run through the back of the scanner bore. All images passed visual inspection and showed no obvious distortions or interference from RF noise or proximity to electrode wires.

Rating Scales. As described in the main text of the manuscript, volunteers rated sensation intensity and discomfort after both active and sham tDCS condition. Text was presented on a screen as follows for intensity "Please rate the intensity of any sensations felt during previous scan (e.g., tingling, itching, heating, etc. under or near electrodes)". A 10-point Likert scale was used, where 1 indicated "None (No sensations)" and 10 indicated "Worst I can imagine". The following text was used for discomfort: "Please indicate whether sensations were uncomfortable during the previous scan". Again, a 10-point scale was used, where 1 indicated "None (No discomfort)" and 10 indicated "Worst I can imagine".

Statistical Analysis Tools. All statistical analyses were completed in R (https://www.r-project.org) using a number of packages (i.e., libraries). Linear mixed effects models were implemented with the lme4 package [4]. Post-hoc contrasts were estimated using emmeans [5] in two cases: (1) pairwise comparisons of tDCS conditions in nodes and/or networks meeting statistical criteria for "significance" in the primary and secondary analyses described in the main methods text and (2) in the secondary analysis, which used planned *post hoc* contrasts of active tDCS and sham tDCS in montage-specific E field hot spots. Linear models (i.e., associations with tDCS ratings) were implemented with R's native stats package. In all statistical models, factors were either numeric (e.g., node-to-network FC, age) or categorical (e.g., montage, condition). Cortical surfaces were read and written using cifti package for R [6] and displayed in Connectome Workbench for visualization purposes in figures. Plots were created using gglot2 package for R [7].

Statistical Analysis: P-Values and Effect Size. Whether and how it is appropriate to estimate p-values and effect sizes in linear mixed-effects models is a matter of debate amongst statisticians [4], [8], [9]. In our study, we used the Kenward-Roger approximation of degrees of freedom to estimate F and p statistics for our models [8]. For effect sizes, we include detailed descriptive statistics for all effects reaching statistical criterion in Supplementary Tables 1,3,4, specifically mean, standard deviation, and 95% confidence interval for each condition. These could be used to facilitate future meta-analyses and power calculations (e.g., to calculate Cohen's d or other proxies for effect size of the target effect). Data associated with these descriptive statistics are also available to researchers upon request.

References used in Supplemental Material

[1] J. M. Bhatt, N. Bhattacharyya, and H. W. Lin, “Relationships between tinnitus and the prevalence of anxiety and depression,” *The Laryngoscope*, vol. 127, no. 2, pp. 466–469, 2017, doi: https://doi.org/10.1002/lary.26107.

[2] M. A. Nitsche and W. Paulus, “Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation,” *J. Physiol.*, vol. 527, no. Pt 3, pp. 633–639, Sep. 2000, doi: 10.1111/j.1469-7793.2000.t01-1-00633.x.

[3] M. A. Nitsche and W. Paulus, “Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans,” *Neurology*, vol. 57, no. 10, pp. 1899–1901, Nov. 2001, doi: 10.1212/wnl.57.10.1899.

[4] Bates, Douglas, Mächler, Matin, Bolker, Ben, and Walker, Steve, “Fitting Linear Mixed-Effects Models Using lme4,” *J. Stat. Softw.*, vol. 67, no. 1, 2015, doi: 10.18637/jss.v067.i01.

[5] R. V. Lenth, *rvlenth/emmeans*. 2020. Accessed: Oct. 07, 2020. [Online]. Available: https://github.com/rvlenth/emmeans

[6] J. Muschelli, *cifti: Toolbox for Connectivity Informatics Technology Initiative ('CIFTI') Files*. 2018. Accessed: Oct. 07, 2020. [Online]. Available: https://CRAN.R-project.org/package=cifti

[7] H. Wickham, *ggplot2: Elegant Graphics for Data Analysis*. New York: Springer-Verlag, 2016. [Online]. Available: https://ggplot2.tidyverse.org

[8] M. G. Kenward and J. H. Roger, “Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood,” *Biometrics*, vol. 53, no. 3, pp. 983–997, 1997, doi: 10.2307/2533558.

[9] F. E. Satterthwaite, “An Approximate Distribution of Estimates of Variance Components,” *Biom. Bull.*, vol. 2, no. 6, pp. 110–114, 1946, doi: 10.2307/3002019.

SUPPLEMENTAL TABLES

Supplemental Table 1. Representative Nodes Showing Main Effect of tDCS Condition

FC Metric	Node Description	Node Index	Active, All Montages Mean	Active, All Montages SD	Active, All Montages CI	Sham, All Montages Mean	Sham, All Montages SD	Sham, All Montages CI	Rest, All Montages Mean	Rest, All Montages SD	Rest, All Montages CI	Stats, Main Effect of Condition
fALFF	Visual Cortex / Intracalcarine Sulcus	18	0.371	0.046	0.012	0.377	0.044	0.011	0.352	0.037	0.007	F(2,176) = 8.52, p = 0.0003
fALFF	Somatosensory Cortex / Postcentral Gyrus	27	0.347	0.054	0.013	0.358	0.055	0.014	0.331	0.046	0.008	F(2,176) = 8.97, p = 0.0002
fALFF	Auditory Cortex / Heschl's Gyrus	45	0.271	0.041	0.010	0.278	0.039	0.010	0.261	0.031	0.006	F(2,176) = 6.87, p = 0.001
fALFF	Posterior Cingulate / Precuneus	189	0.230	0.033	0.008	0.244	0.035	0.009	0.226	0.028	0.005	F(2,176) = 7.95, p = 0.0005
fALFF	Dorsal Anterior Cingulate	312	0.223	0.020	0.005	0.229	0.021	0.005	0.219	0.019	0.003	F(2,176) = 5.16, p = 0.007
ReHo	Visual Cortex / Lingual Gyrus	15	0.759	0.040	0.010	0.772	0.042	0.010	0.750	0.041	0.007	F(2,176) = 8.01, p = 0.0005
ReHo	Somatosensory Cortex / Postcentral Gyrus	27	0.787	0.048	0.012	0.801	0.050	0.012	0.776	0.049	0.009	F(2,176) = 7.88, p = 0.0005
ReHo	Superior Parietal Lobule	81	0.740	0.039	0.010	0.759	0.038	0.009	0.735	0.038	0.007	F(2,176) = 9.45, p = 0.0001

Confidence Intervals (CI) calculated using within-subjects method. Asterisks next to node index are nodes also marked with asterisks in Figure 2.

Supplemental Table 2. Top 5 High E Field Nodes for Each Montage

Montage	Node Index	Node Description	Network Index	Network Description
DLPFC	316	Right Orbitofrontal Cortex	10	Orbitofrontal
	306	Right Dorsolateral Prefrontal Cortex	8	Frontoparietal 2
	313	Right Orbitofrontal Cortex	10	Orbitofrontal
	348	Right Inferior Frontal Gyrus	13	Frontoparietal 1
	347	Right Inferior Frontal Gyrus	13	Frontoparietal 1
LTA	336	Right Mid Middle Temporal Gyrus	13	Frontoparietal 1
	56	Left Precentral Gyrus	4	Auditory & Ventral Somatomotor
	54	Left Precentral Gyrus	4	Auditory & Ventral Somatomotor
	358	Right Anterior Middle Temporal Gyrus	16	Default Mode
	392	Right Anterior Superior Temporal Sulcus	14	Superior Temporal Sulcus
STC	336	Right Mid Middle Temporal Gyrus	13	Frontoparietal 1
	170	Left Anterior Superior Temporal Sulcus	17	Frontoparietal 3
	168	Left Anterior Middle Temporal Gyrus	17	Frontoparietal 3
	169	Left anterior Middle Temporal Gyrus	17	Frontoparietal 3
	392	Right Anterior Superior Temporal Sulcus	14	Superior Temporal Sulcus

Supplemental Table 3. Effects of Active tDCS on Functional Connectivity (FC) in High E Field Networks

		Active DLPFC-tDCS			Sham DLPFC-tDCS			Stats, DLPFC-tDCS				Active LTA-tDCS			Sham LTA-tDCS			Stats, LTA-tDCS				Active STC-tDCS			Sham STC-tDCS			Stats, STC-tDCS			
Effect	FC metric	Mean	SD	CI	Mean	SD	CI	beta	beta SE	t	p	Mean	SD	CI	Mean	SD	CI	beta	beta SE	t	p	Mean	SD	CI	Mean	SD	CI	beta	beta SE	t	p
DLPFC Active vs. Sham	Orbitofrontal Network (RSN10)	0.38	0.64	0.21	0.02	0.55	0.18	0.36	0.11	3.11	0.0022*	-0.46	0.60	0.32	-0.26	0.73	0.39	-0.21	0.17	-1.18	0.24	0.29	0.27	0.18	0.17	0.29	0.20	0.12	0.21	0.56	0.58
DLPFC Active vs. Sham	sgACC (Node317) with Frontoparietal 1 (RSN13)	0.14	4.78	1.59	-3.52	4.51	1.51	3.69	0.96	3.83	0.0002*	0.17	2.70	1.44	-0.44	2.18	1.16	0.61	1.46	0.42	0.68	-2.65	2.74	1.84	-2.05	3.91	2.62	-0.59	1.77	-0.34	0.74
DLPFC Active vs. Sham	SPL (Node266) with Frontoparietal 1 (RSN13)	-1.48	12.24	4.08	-14.15	14.21	4.74	12.58	3.03	4.15	0.0001*	-3.10	6.74	3.59	-6.26	12.03	6.41	3.16	4.61	0.69	0.49	4.77	13.67	9.18	-2.63	11.93	8.02	7.40	5.56	1.33	0.18
LTA Active vs. Sham	FOp (Node106) with Auditory & Ventral Somatomotor (RSN4)	3.38	8.91	2.97	1.98	8.86	2.96	1.38	1.80	0.77	0.44	-6.44	7.80	4.16	4.00	7.80	4.16	-10.74	2.74	-3.81	0.0002*	0.00	7.44	5.00	0.74	8.94	6.01	-0.74	3.30	-0.22	0.82
LTA Active vs. Sham	LOC (Node261) with Default Mode (RSN16)	10.99	11.72	3.91	13.87	14.13	4.71	-0.91	1.46	-0.63	0.53	3.42	15.28	8.14	21.37	18.64	9.93	-8.91	2.22	-4.02	0.0001*	8.13	7.37	4.95	8.66	7.07	4.75	-1.36	2.67	-0.51	0.61
STC Active vs. Sham	TP (Node323) with Frontoparietal 3 (RSN17)	-2.42	4.07	1.36	-3.42	4.67	1.56	1.00	0.88	1.13	0.26	-2.51	3.30	1.76	-1.02	4.15	2.21	-1.49	1.34	-1.10	0.27	0.11	2.89	1.94	-5.50	3.87	2.60	5.61	1.62	3.46	0.0007

**Asterisks mark stats meeting criterion pFDR < 0.05 in the main analysis*

Supplemental Table 4. Mean FC in Regions Showing Associations with tDCS Ratings

				Stats			Active, All Montages			Sham, All Montages			Rest, All Montages		
Rating	FC Metric	Node Description	Node Index	beta(SE)	t	p	Mean	SD	CI	Mean	SD	CI	Mean	SD	CI
Intensity	RSN6	Visual Cortex	19	-4.432(1.086)	-4.081	0.00009	1.944	13.372	3.340	4.450	13.077	3.267	3.359	15.310	2.791
Intensity	RSN6	Dorsal PMC	40	-5.845(1.457)	-4.013	0.0001	-2.009	20.740	5.181	-1.573	18.711	4.674	-2.029	21.317	3.886
Discomfort	fALFF	LOC	10	-0.016(0.003)	-4.081	0.0000004	0.335	0.038	0.010	0.341	0.040	0.010	0.328	0.032	0.006
Discomfort	fALFF	LOC	64	-0.018(0.003)	-5.560	0.00000008	0.314	0.034	0.008	0.317	0.042	0.010	0.306	0.035	0.006
Discomfort	fALFF	Posterior STS / AG	173	-0.013(0.002)	-5.359	0.0000002	0.298	0.030	0.007	0.304	0.034	0.008	0.295	0.025	0.005
Discomfort	fALFF	Posterior STS	375	-0.011(0.007)	-4.449	0.00001	0.327	0.028	0.007	0.328	0.033	0.008	0.320	0.027	0.005
Discomfort	fALFF	Posterior STS	396	-0.014(0.003)	-5.160	0.0000006	0.311	0.027	0.007	0.317	0.033	0.008	0.308	0.028	0.005

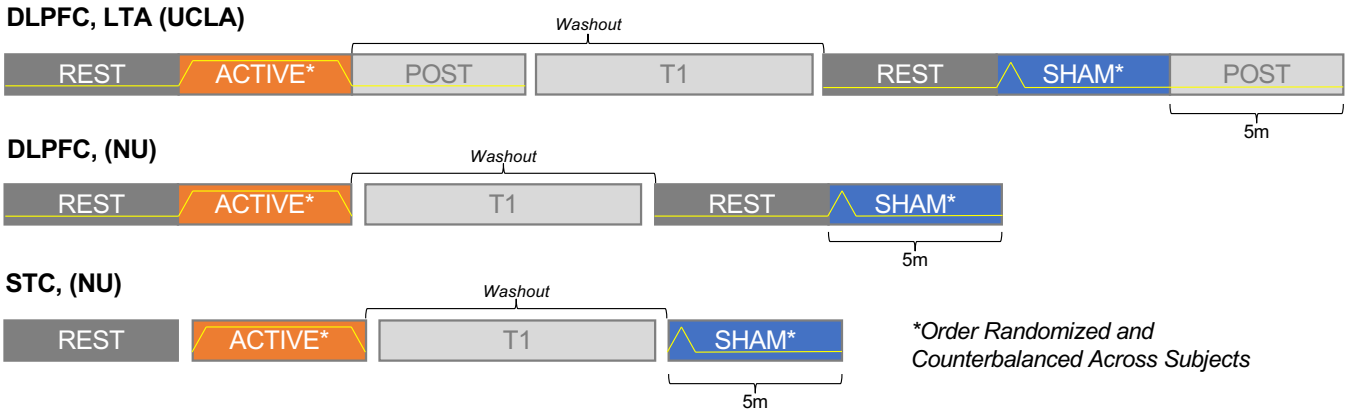
Confidence Intervals (CI) calculated using within-subjects method. Abbreviations: Premotor Cortex, PMC; Lateral Occipital Cortex, LOC; Superior Temporal Sulcus, STS; Angular Gyrus, AG

Supplemental Table 5. Effects of Site on Target Analyses

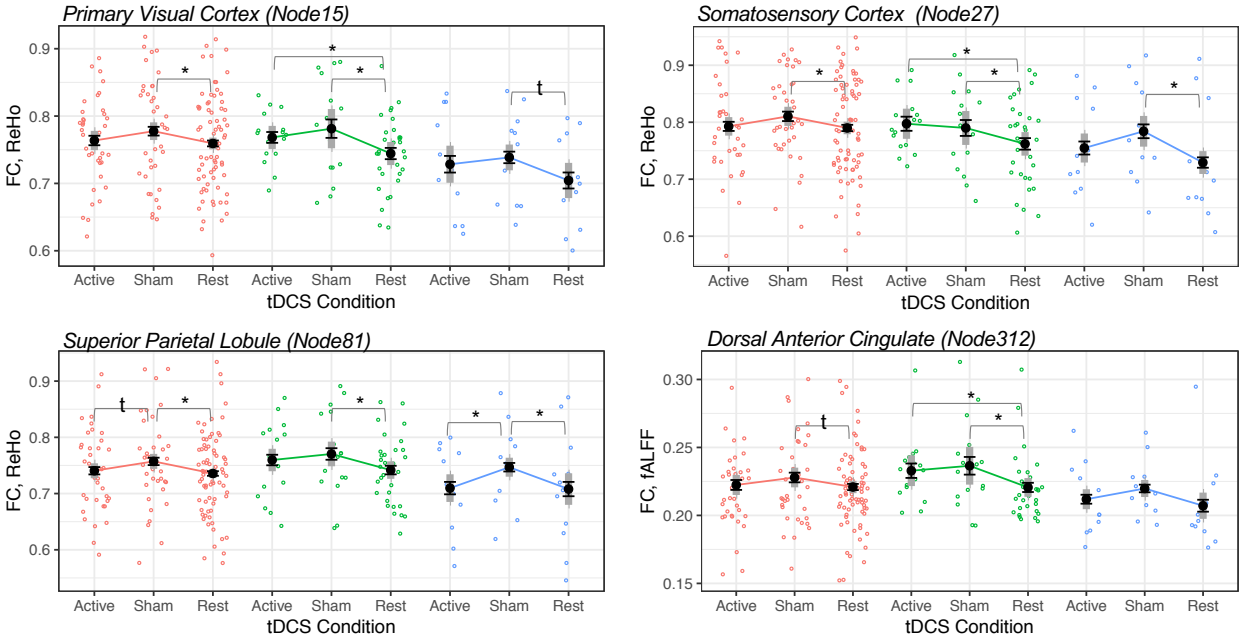
Effect	FC metric	Location of Original Target Stats	Stats, Target Effect with Site Covariate	Stats, Main Effect of Site
Main Effect of Condition	fALFF in Visual Cortex / Intracalcarine Sulcus (Node18)	Suppl Table 1	F(2,176) = 8.52, p = 0.0003	F(1,59) = 0.00, p = 0.99
Main Effect of Condition	fALFF Somatosensory Cortex / Postcentral Gyrus (Node27)	Suppl Table 1	F(2,176) = 9.00, p = 0.0002	F(1,58) = 0.42, p = 0.52
Main Effect of Condition	fALFFAuditory Cortex / Heschl's Gyrus (Node45)	Suppl Table 1	F(2,176) = 6.87, p = 0.001	F(1,59) = 0.15, p = 0.70
Main Effect of Condition	fALFF in Posterior Cingulate / Precuneus (Node189)	Suppl Table 1	F(2,176) = 7.98, p = 0.0005	F(1,59) = 1.70, p = 0.20
Main Effect of Condition	fALFF in Dorsal Anterior Cingulate (Node312)	Suppl Table 1	F(2,176) = 5.17, p = 0.007	F(1,58) = 0.24, p = 0.62
Main Effect of Condition	ReHo in Visual Cortex / Lingual Gyrus (Node15)	Suppl Table 1	F(2,176) = 8.01, p = 0.0005	F(1,58) = 1.64, p = 0.21
Main Effect of Condition	ReHo in Somatosensory Cortex / Postcentral Gyrus (Node27)	Suppl Table 1	F(2,176) = 7.88, p = 0.0005	F(1,58) = 0.25, p = 0.62
Main Effect of Condition	ReHo in Superior Parietal Lobule (Node81)	Suppl Table 1	F(2,176) = 9.45, p = 0.0001	F(1,58) = 0.00, p = 0.98
DLPFC Active vs. Sham	Orbitofrontal Network (RSN10)	Suppl. Table 3	beta(SE) = 0.357(0.115), p = 0.002	F(1,57)=2.59, p=.11
DLPFC Active vs. Sham	sgACC (Node317) with Frontoparietal 1 (RSN13)	Suppl. Table 3	beta(SE) = 3.69(0.96), p = 0.0002	F(1,56) = 2.78, p = 0.10
DLPFC Active vs. Sham	SPL (Node266) with Frontoparietal 1 (RSN13)	Suppl. Table 3	beta(SE) = 12.58(3.03), p = 0.0001	F(1,58) = 0.009, p = 0.93
LTA Active vs. Sham	FOp (Node106) with Auditory & Ventral Somatomotor (RSN4)	Suppl. Table 3	beta(SE) = -10.44(2.74), p = 0.0002	F(1,56) = 0.092, p = 0.76
LTA Active vs. Sham	LOC (Node261) with Default Mode (RSN16)	Suppl. Table 3	beta(SE) = -17.95(4.18), p < 0.0001	F(1,59) = 0.024, p = 0.88
STC Active vs. Sham*	TP (Node323) with Frontoparietal 3 (RSN17)	Suppl. Table 3	beta(SE) = 5.61(1.62), p = 0.0007	F(1,58) = 1.77, p = 0.19
Intensity Ratings	RSN6 with Visual Cortex (Node19)	Suppl. Table 4	beta(SE) = -4.01(1.12), p = 0.0004	beta(SE) = 5.74(4.52), p = 0.21
Intensity Ratings	RSN6 with Dorsal PMC (Node40)	Suppl. Table 4	beta(SE) = -5.70(1.51), p = 0.0003	beta(SE) = 2.43(6.10), p = 0.69
Discomfort Ratings	fALFF in LOC (Node10)	Suppl. Table 4	beta(SE) = -0.12(0.003), p = 0.000005	beta(SE) = 0.007(0.010), p = 0.50
Discomfort Ratings	fALFF in LOC (Node64)	Suppl. Table 4	beta(SE) = -0.017(0.003), p = 0.000002	beta(SE) = 0.011(0.011), p = 0.29
Discomfort Ratings	fALFF in Posterior STS / AG (Node173)	Suppl. Table 4	beta(SE) = -0.014(0.003), p = 0.000001	beta(SE) = -0.002(0.008), p = 0.81
Discomfort Ratings	fALFF in Posterior STS (Node375)	Suppl. Table 4	beta(SE) = -0.011(0.003), p = 0.00005	beta(SE) = 0.001(0.008), p = 0.93
Discomfort Ratings	fALFF in Posterior STS (Node396)	Suppl. Table 4	beta(SE) = -0.013(0.003), p = 0.00001	beta(SE) = 0.009(0.009), p = 0.32

**Stats for this effect did not meet criterion pFDR < 0.05 in the main analysis, but are reported here for completeness.*

Supplemental Figure 1. Schematic of Stimulation Protocols Across Sites. In each case, Rest (no stim) was presented first. Order of active and sham conditions was randomized and counterbalanced across subjects. Active and sham conditions were separated by a T1-weighted anatomical scan (8m) and post-scan questions and instructions (~2m). Each condition (rest/active/sham) was 5 minutes long. Data associated with post-stim BOLD-fMRI was not analyzed for this study. Stimulus waveforms for active and sham tDCS conditions are also overlaid in yellow, including linear 30s on- and off-ramps.



Supplemental Figure 2. Main Effect of tDCS Condition in Representative Nodes. Plots complement Figure 1.



Supplemental Figure 3. Decreased FC in High E Field Networks during STC-tDCS, p<0.001. Plots complement Figure 4.