Frontopolar Transcranial Direct Current Stimulation Alters Intrinsic Functional Connectivity during Resting-State fMRI

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RESEARCH BACKGROUND

- The frontopolar prefrontal cortex (FPC) has been implicated in high-order cognitive functions such as integrating relationship information, memory retrieval, and attentional reallocation (Ramnani & Owen, 2004) .
- Transcranial direct current stimulation (tDCS) has largely been proposed to modulate brain functional connectivity in a non-invasive way. There are, however, only few neuroimaging studies that have evaluated the effects of tDCS directly targeting the FPC.
- The present study investigated whether both tDCS electrodes arrangement on the FPC would induce changes in functional connectivity of intrinsic brain networks measured by functional magnetic resonance imaging (fMRI).
- Relatively small electrodes (12.5 cm^2) compared to conventional ones (35 cm^2) were used in order to constrain electric field induced by tDCS exclusively to the FPC.

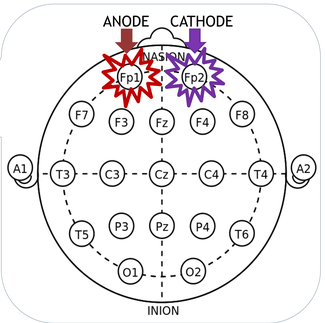
EXPERIMENTAL PROCEDURE

- **Participants**
  - Active tDCS Group (N=20, 12 males, mean age=25.9)
  - Sham tDCS Group (N=20, 12 males, mean age=25.4)

- **Experimental Procedure**

SCAN PROTOCOL
3T Philips, T2* weighted single shot EPI sequence
TR=2000ms, TE=30ms, 33 axial slices, 30° oblique to AC-PC line

Resting-State fMRI (10 minutes) → tDCS (15 minutes) → Resting-State fMRI (10 minutes) → Questionnaires (5 minutes)



- **tDCS Application**
  - 3.5 x 3.5 cm^2 saline soaked sponge electrodes connected to a direct current stimulator (Foc.us)
  - Anode on the left FPC (FP1 according to EEG 10-20 system)
  - Cathode on the right FPC (FP2 according to EEG 10-20 system)
  - 15 minutes, 0.5mA
  - Sham tDCS : stimulation was applied at 0.5mA, but turned off 30s after start without noticing participants.

References

1. Ramnani, N., & Owen, A. M. (2004). Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. Nature reviews. Neuroscience, 5(3), 184.
2. Dosenbach, N. U., Nardos, B., Cohen, A. L., Fair, D. A., Power, J. D., Church, J. A., ... & Barnes, K. A. (2010). Prediction of individual brain maturity using fMRI. Science, 329(5997), 1358-1361.
3. Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., ... & Petersen, S. E. (2011). Functional network organization of the human brain. *Neuron*, 72(4), 665-678.

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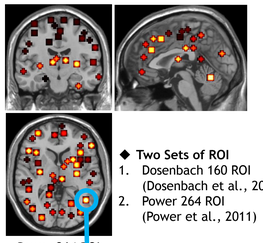
fMRI ANALYSIS 1. functional connectivity Multivariate Pattern Analysis (fcMVPA)

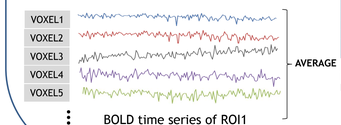
1. Node Selection



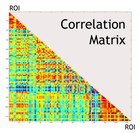
◆ **Two Sets of ROI**
1. Dosenbach 160 ROI (Dosenbach et al., 2010)
2. Power 264 ROI (Power et al., 2011)

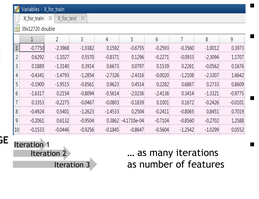
<Power 264 ROI>

2. ROI Mean Time-Series Extraction



3. fcMVPA





METHODS

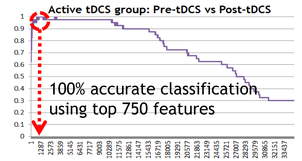
◆ Feature Calculation
- Pair-wise cross-correlation between each ROI time series were calculated (Pearson's *r*). Fisher's *z*-transformation was then applied to the correlation coefficients. Fisher's *z* transformed correlation values were used as features in subsequent fcMVPA.
- Independent two sample *t*-test was conducted to compare features of the active and sham tDCS group. Paired *t*-test was also conducted to compare features of pre- and post- tDCS in active tDCS group. Leave-one-out cross validation (LOOCV) was applied and features were ranked based on average absolute *t*-score.

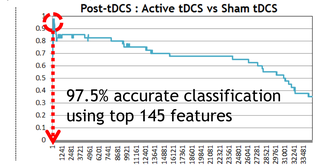
◆ Group Classification using Support Vector Machine (SVM) Algorithm
- By iteration, each feature was added cumulatively in descending order of *t*-value.
- LOOCV was applied; features of a participant was used as test data while those of rest of participants were used as training data for SVM group classification.
- Whole iteration was repeated for the number of participants so that every participant could be used as test data.
- Classification accuracy was calculated based on classification performance indicating whether test data was correctly classified into a certain group using combination of included features.
- Permutation tests were performed (n=100).

RESULTS

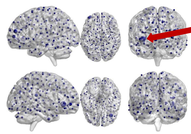
◆ Classification Accuracies
- Classification accuracies indicate how successfully the combination of included features discriminated two groups.
- Peak Classification Accuracy (Power 264 ROI were used)

1. Active tDCS group: Pre-tDCS vs Post-tDCS (97.5% accurate, using top 145 features)
2. Post-tDCS : Active tDCS vs Sham tDCS (100% accurate, using top 750 features)

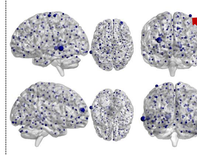




◆ Betweenness Centrality (BC) of Regions that Elicited Peak Classification Accuracy



MNI(x)	MNI(y)	MNI(z)	Region Name	BC
37	32	-2	Right Inferior Orbitofrontal Cortex	0.13
-39	51	17	Left Mid Frontal Gyrus	0.07
-34	55	4	Left Mid Frontal Gyrus	0.05
65	-33	20	Right Superior Temporal Gyrus	0.05
43	49	-2	Right Mid Orbitofrontal Cortex	0.05
-7	51	-1	Left Anterior Cingulate Cortex	0.04
49	-3	-38	Right Inferior Temporal Gyrus	0.03

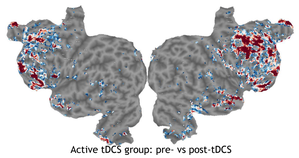


MNI(x)	MNI(y)	MNI(z)	Region Name	BC
-13	-40	1	Left Precuneus	0.16
31	56	14	Right Mid Frontal Gyrus	0.14
-68	-41	-5	Left Mid Temporal Gyrus	0.12
-58	-30	-4	Left Mid Temporal Gyrus	0.09
-38	-27	69	Left Postcentral Gyrus	0.03
19	-8	64	Right Superior Frontal Gyrus	0.02
35	-67	-34	Cerebellum	0.02

fMRI ANALYSIS 2. Altered Seed-Based FC, ReHo, ALFF

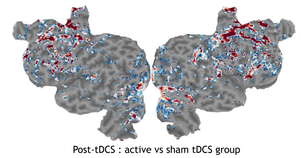
◆ (1) Active tDCS group : Pre- vs Post-tDCS (left), (2) Post-tDCS : Active vs Sham tDCS group (right)

Functional Connectivity (FC) with FP1



After active tDCS, (paired *t*-test, $p < 0.05$)
1.Increase of FP1-based FC in the bilateral **precuneus**, parahippocampal gyrus, **middle cingulate cortex**, paracentral lobule, supplementary motor area (SMA) and inferior parietal lobe.

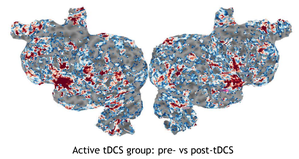
2.Decrease of FP1-based FC in the **right superior frontal gyrus, superior orbitofrontal cortex (OFC) and middle frontal gyrus.**



Compared to sham tDCS, (two sample *t*-test, $p < 0.05$)
1. Greater FP1-based FC in the SMA.

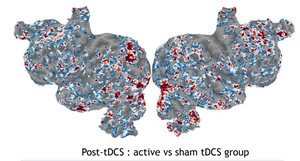
2. Less FP1-based FC in the **superior medial frontal gyrus** , middle cingulate cortex, ACC, pallidum, **middle OFC,** superior temporal pole and inferior temporal gyrus.

Regional Homogeneity (ReHo)



After active tDCS, (paired *t*-test, $p < 0.05$)
1. Increase of ReHo in the bilateral superior parietal sulcus, **superior medial frontal gyrus,** precentral gyrus and **superior frontal gyrus.**

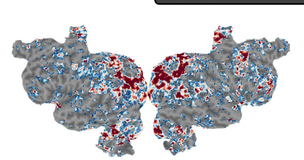
2. Decrease of ReHo in the bilateral insula, inferior OFC, thalamus, middle cingulate cortex, ACC and SMA.



Compared to sham tDCS, (two sample *t*-test, $p < 0.05$)
1. Greater ReHo in the **superior medial frontal gyrus,** ACC, OFC, insula, inferior temporal gyrus and right fusiform gyrus.

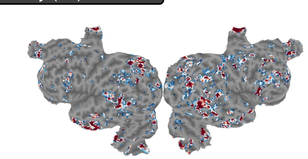
2. Less ReHo in the precentral gyrus, SMA and left fusiform gyrus.

Functional Connectivity (FC) with PCC



After active tDCS (paired *t*-test, $p < 0.05$),
1. Increase of PCC-based FC in the bilateral **superior frontal gyrus,** inferior temporal gyrus, inferior OFC, **medial superior frontal gyrus**, right superior temporal pole and left middle OFC.

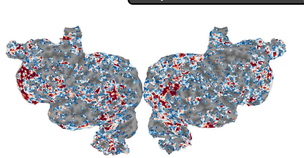
2. Decrease of PCC-based FC in the **middle cingulate cortex** and right thalamus



Compared to sham tDCS, (two sample *t*-test, $p < 0.05$)
1. No significant increase of FC between PCC and other regions.

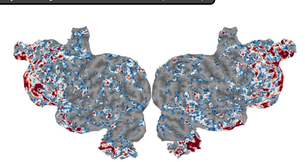
2. Less PCC-based FC in the SMA, middle frontal gyrus and **ACC.**

Amplitude of Low Frequency Fluctuations (ALFF)



After active tDCS, (paired *t*-test, $p < 0.05$)
1. Increase of ALFF in the bilateral middle cingulate cortex, thalamus and middle temporal gyrus.

2. Decrease of ALFF in the bilateral middle occipital cortex, middle frontal gyrus, superior frontal gyrus and ACC.



Compared to sham tDCS, (two sample *t*-test, $p < 0.05$)
1. Greater ALFF in the **bilateral middle OFC**, parahippocampal gyrus, caudate nucleus, **superior medial frontal gyrus** and inferior temporal gyrus.

2. Less ALFF in the precentral gyrus, fusiform gyrus, superior temporal gyrus and middle temporal gyrus.

DISCUSSION

- **Results Summary**
  - Frontopolar tDCS induced alteration of intrinsic functional connectivity networks including both cortical and subcortical regions of the human brain.
  - As expected, alterations of the frontal activities after tDCS were found. The middle frontal gyrus, OFC and superior prefrontal gyrus mainly distinguished functional differences between pre- and post-tDCS period. ReHo and ALFF increased in the medial frontal gyrus after active tDCS.
  - The ACC was one of the main regions that classified functional connectivity patterns of pre- and post-tDCS period and its ReHo increased after tDCS.
  - Subcortical regions such as the caudate nucleus showed changes of activities in ALFF analysis. Overall ALFF of the caudate nucleus increased in the active tDCS group compared to the sham group.

- **Limitations & Further Analyses**
  - Possible individual differences within the same group should be included as a main factor in further analysis. Individuals can be divided into separate groups based on their reports on tDCS adverse effect questionnaire, Barratt Impulsivity Scale, gender and baseline resting-state activities.
  - Participants allocated to the sham tDCS group commonly reported increase of sleepiness after tDCS compared to the active tDCS group. Differences between two groups in post-tDCS period might have been induced by different sleepiness levels of two groups.
  - We found altered activities of DMN hub regions such as the medial prefrontal gyrus and PCC/precuneus after active tDCS which could refer to changes of task-related brain networks and behavior.
  - We would further select a few regions of interest (ROI) and investigate more specific alterations within ROI.