NYC Neuromodulation 2020 Online

Neuromodulation for Responders vs. Non-Responders:

Stimulation of the premotor cortex enhances inter-hemispheric functional connectivity in moderate-to-severe chronic stroke, but not for those with mild impairment

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Transcranial direct current stimulation (tDCS) in stroke rehabilitation

- tDCS is used to augment rehabilitation outcomes for stroke motor recovery
- tDCS targeting the lesioned primary motor cortex (iM1) aims to augment rehabilitation outcomes
  - Can enhance corticospinal excitability and motor re-learning
- Promising early trials; meta-analyses demonstrate conflicting results
- Limited efficacy of iM1 tDCS in studies including participants with wide variability in motor impairment

Hankey et al. *Stroke* (2002); Hao Z et al. *Cochrane Database Syst. Rev.* (2013)

Premotor cortex (PMC)

- Potential to recruit widespread cortical circuitry for recovery of motor function
  - Higher likelihood of survival
  - Direct alternate contributions to descending corticospinal tract + uncrossed, ipsilateral motor pathways
  - Dense intra- and inter-hemispheric connections to intact motor areas in the contralesional hemisphere

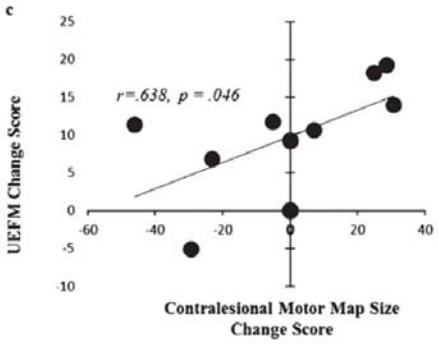
M1 PMC

Transcallosal tracts connecting homologous M1 and PMC.

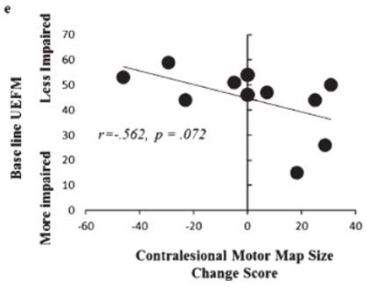
Ruddy et al. *Brain Struct Funct* (2017).

Marconi et al. *Eur J Neurosci* (2003); Plow et al. *Neuroscientist* (2015)

Anodal iPMC tDCS may augment rehabilitation outcomes



Δ UEFM associated with ↑ excitability of nonlesioned hemisphere



Baseline UEFM associated with Δ excitability of nonlesioned hemisphere

Cunningham et al. *RNN* (2015)

Distinct mechanisms of recovery

- Patients with varying levels of stroke-related impairment may undergo distinct cortical adaptations to regain motor function
- Mild impairments:
  - Benefit from restored influence of iM1
- More severe impairments:
  - Rely on intact substrates in the contralesional hemisphere due to extensive damage to pathways from iM1

Objective: to determine if iPMC stimulation promotes widespread connectivity in association with improvements in motor impairment and to determine if its benefits are influenced by baseline motor severity

Di Pino et al. *Nat Rev Neurol* (2014)

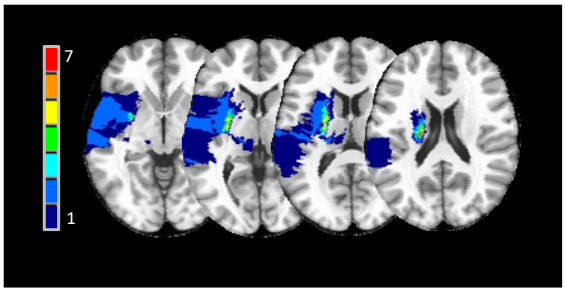
Hypotheses

- iPMC tDCS may enhance **inter-hemispheric** functional connectivity (FC) between the ipsilesional and the (intact) contralesional motor regions in participants with more **severe motor impairment**

- iPMC tDCS may enhance **intra-hemispheric** FC in participants with **mild motor impairment** given that they have sufficient substrates remaining

Participants

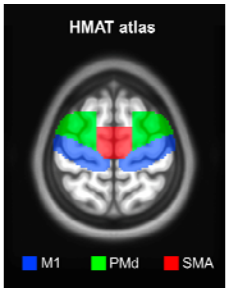
- Patients >6 months after 1st stroke (ischemic or hemorrhagic)
  - Impairment-matched + randomized to receive iPMC or sham tDCS
  - Motor impairment assessed using the Upper Extremity Fugl-Meyer (UEFM) assessment
  - UEFM cutoff 47 to separate participants with mild vs. moderate-severe impairment (Woodbury et al 2013)
- 17/25 trial participants had sufficient imaging data
- Mean age, 62.6 ± 9.5 years
- Median 29 months post-stroke
- Mean UEFM, 43 ± 12 (normal 66)
  - 11 moderate-severe; 6 mild
- No differences in baseline characteristics between tDCS (N=7) and sham (n=10) groups

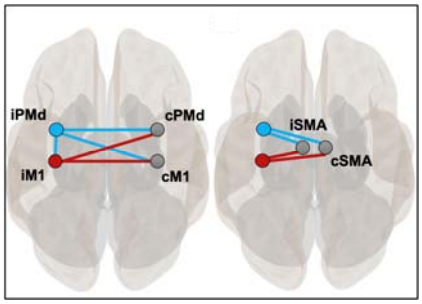


Stroke lesions in MNI space.

Functional connectivity (FC) analysis

- Rs-fMRI preprocessed using MATLAB and AFNI
- Human Motor Area Template (HMAT) atlas to define motor area boundaries:
  - Primary motor cortices (M1)
  - Dorsal premotor cortices (PMd)
  - Supplementary motor areas (SMA)
- Task-based fMRI (opening and closing paretic hand) for seed localization
- Studied FC between 9 region of interest (ROI) pairs

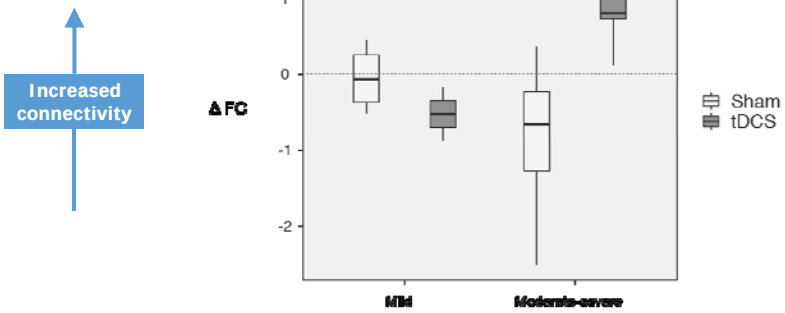


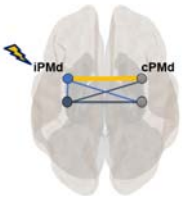


Region of interest (ROI) pairs.

Mayka et al. *Neuroimage* (2006)

Increase in inter-hemispheric FC

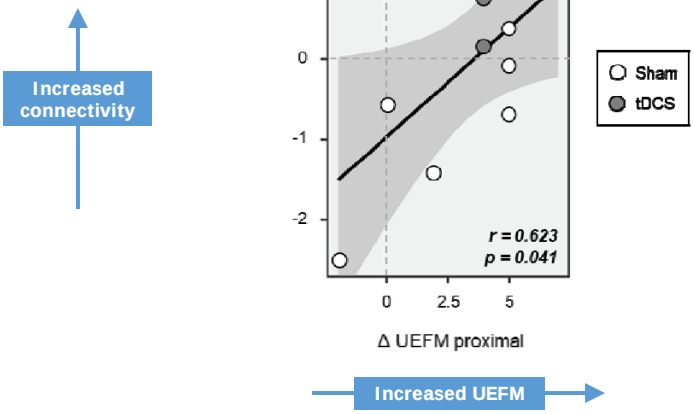


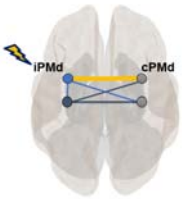


iPMd-cPMd FC increased with tDCS in the moderate-severe sub-group

Significant 3-way interaction between Intervention Group, Severity Level, and Time on iPMd-cPMd FC (p = 0.015)

Correlation with motor impairment

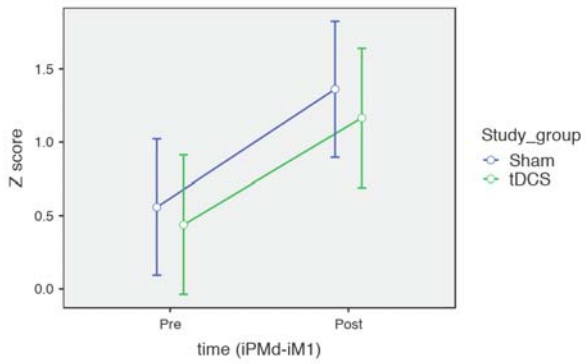


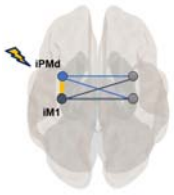


Correlated with improved motor outcome in moderate-severe sub-group

Increase in intra-hemispheric FC

Increased connectivity



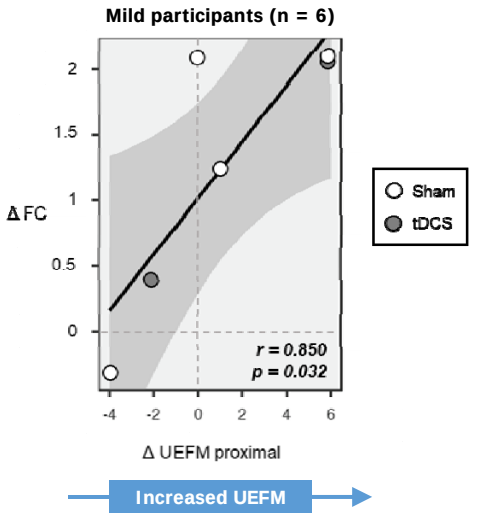


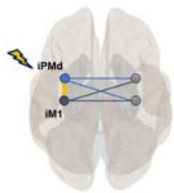
iPMd-iM1 FC increased regardless of tDCS or sham stimulation

Significant main effect of Time on iPMd-iM1 FC ($p = 0.022$)

Correlation with motor impairment

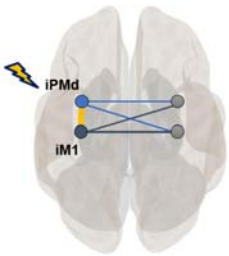
Increased connectivity





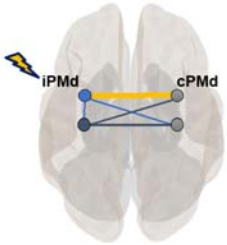
Correlated with improved motor outcome in mild sub-group

Intra-hemispheric FC



- Increased regardless of tDCS or sham stimulation
- Associated with improvements in proximal motor impairment only in participants with **mild** baseline motor impairment

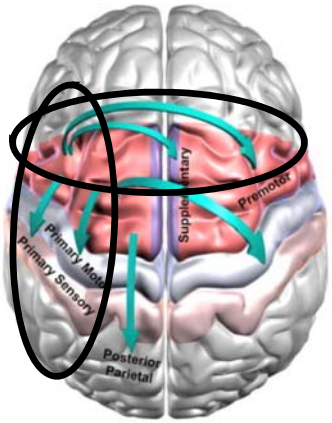
Inter-hemispheric FC



- Increased with tDCS only in the moderate-severe sub-group
- Associated with improvements in proximal motor impairment within the **moderate-severe** sub-group

Discussion

- Facilitating iPMC may increase connectivity through PMC's dense transcallosal connections
  - Intact hemisphere supports recovery of the ipsilateral paretic limb in patients with more severe impairments
- CIMT alone may be effective at recruiting the residual networks located in the ipsilesional hemisphere
  - Increased connectivity was associated with recovery for the mildly impaired
    - No additional benefit of tDCS: Ceiling effect
  - The moderate-to-severely impaired lack viable ipsilesional substrate
- Our findings support the growing literature to personalize stimulation based on intrinsic mechanisms of recovery for patients with different ranges of impairment



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