The Potential and Limitations of Transcranial Direct Current Stimulation

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tDCS: transcranial Direct Current Stimulation

Cathode (-) Electrode
Anode (+) Electrode

20 minute session 5x per week

“Anodal” / “Cathodal” refer to proximity of target
"Cathodal" tDCS
Soma hyper-polarized
Apical dendrite depolarized

"Anodal" tDCS
Soma depolarized
Apical dendrite hyper-polarized
tDCS is the most investigated therapeutic technology in neuropsychiatry...

>300 active trials ClinicalTrials.gov

>600 pubs per year

Depression, Pain, Schizophrenia, ADHD, PTSD, Alzheimer’s, Addiction...

...where questions continue to arise if it works at all.
tDCS: Status

Panacea

Snake Oil

It’s complicated.
Simplicity in tDCS technology does not justify trivial simplistic mechanisms of action or lack of sophistication in use.

That tDCS in its mode of application, mechanisms, and outcomes is complicated is not a deficiency, but inevitable given complexity of brain (dys)function.
tDCS

M1-SO tDCS montage

High Definition tDCS

Experimentally-verified Anatomical MRI derived models of current flow


4x1 HD-tDCS montage
tDCS

Circuit Therapeutics

High Definition tDCS

Non-invasive Targeted

M1-SO tDCS montage

4x1 HD-tDCS montage

Experimentally-verified Anatomical MRI derived models of current flow

Different tDCS electrode montages may be as functionally distinct as different drugs

Different anatomy $\rightarrow$ Different brain current flow.

Including for atypical anatomy (neurodegenerative disorders, brain injury), extremes of age...

When applying the same tDCS across a population, aggregate response reflect individual variability.

Gyri level changes in outward/inward polarity

TMS is used a probe on motor excitability.

Orientation of TMS and tDCS controlled.

Significant changes in cortical excitability by tDCS - but highly pathway specific.

Rawji, Rothwell et al. tDCS changes in motor excitability are specific to orientation. Brain Stim. 2018
Analysis of tDCS must be based on (individual) brain current flow, not just “nominal” target. (and gyri-level modeling tools for this exist, e.g. NIMH “ROAST”)

Brain effects of tDCS are pathway specific (collapsing across different tDCS approaches and outcomes can produce null meta-analysis)

That tDCS is low intensity is not news. And is a mechanistic virtue.
tDCS

From Anatomical Targeting to Task Targeting

Network of interest (e.g. depression, pain network)

Other networks – not targets for neuromodulation

Current flow across entire region

Functional Targeting

Preferential modulation of selected active neurons

Synaptic efficacy is modulated by Direct Current (pathway + polarity specific)

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- Direct Current stimulation does not generate synaptic activity or neuronal firing (Functional Targeting)

Theta Burst Stimulation (TBS) generates LTP which is modulated by concurrent Direct Current Stimulation (DCS)

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1 hour after TBS

• DCS does generate synaptic plasticity de novo (Functional Targeting)

Repeated DCS accelerates LTP and boosts the ceiling for synaptic learning

- Hypothesis: Combing Direct Current stimulation with ongoing training of a task may enhance the rate and ceiling learning specifically of that task (Functional Targeting)

Bikson et al. Origin of specificity during tDCS: activity-selective mechanisms. Front Human Neuro 2013
tDCS: Optimize both Anatomical + Functional Targeting
It’s complicated... in a way systematically characterized over a decade, and which has not been fully realized in technology and human trials. Ongoing clinical trial provide signals.
Monotonic dose response across scales

Technologies/Outcome measures

- Biophysical Modeling
  - Current flow modeling
  - Neuron model
  - Network model
  - Computational neurostimulation

- Animal Modeling
  - Intracellular recording
  - Voltage sensitive dyes
  - Excitatory Post Synaptic Potential (EPSP)
  - Calcium imaging

- Human Neurophysiology
  - Transcranial Magnetic Stimulation (TMS) / Motor Evoked Potential (MEP)
  - Transcranial Magnetic Stimulation (TMS) / Electroencephalography (EEG)
  - Electroencephalography (EEG)

- Neuroimaging
  - Spectroscopy
  - Functional Magnetic Resonance Imaging (fMRI)
  - Arterial Spin Labeling (ASL)

- Behavioral/Clinical Measures
  - Questionnaire
  - Visual Analogue Scale (VAS)
  - Task performance (rate)

1X Change?  2X Change?  -2X Change?  2X Change?
Any EEG can be automatically “inverted” to an optimal HD-tDCS montage

- Based on decades old hypothesis of reciprocity, but based on head model
- Activity guided targeting, but does not require source localization (!)

Dmochowski, et al. Optimal use of EEG recordings to target active brain areas with tES BioRxIv 2016
Home-based extended therapy
1) Better for subjects, Better for operators. Convenience and volume of sessions.
2) Digital therapeutics. Apps and Web-based therapy. Task-control (engage network)
3) Integrated sensors / wearables (biomarkers, feedback targets engaged networks).
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Largest meeting spanning neuromodulation and digital healthcare. Dynamic format from basic science, to clinical trials, to technology. Hand-on Courses and Workshops.
• Input / Output sensitive to anodal polarization only

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• On a population level net change in mixed polarization