Closed looped stimulation: Why bother?

Marom Bikson
Lucas Parra, Jacek Dmochowski, Abhishek Datta, Dennis Truong, Niranjan Khadka, Dennis Truong, Louis Zannou, Zeinab Esmaeilpour, Nigel Gebodh, Belen Lafon, Gozde Unal, Mohamad Rad, Andy Huang

Fifth International Network on tES fMRI (INTF) Webinar
Topic: Individually Optimized Non-Invasive Brain Stimulation
Thursday, May 27th, 2021, 10:00 AM – 12:00 PM (ET, New York Time)
Disclosure

Support
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Neuromodulation is individualized

• Individual patients do better when provided a custom neuromodulation dose.*
• As symptoms (brain state) changes, so can the optimal dose.

*Dose is defined by what given, not by the decision process. (Fundamentals of transcranial electric and magnetic stimulation dose. Brain Stimulation. 2012)

Dose is titrated (on the scale of device design, clinical trials, individual treatment, responsive stimulation)
Decisions to change dose based on
1) Clinical endpoints
2) Biomarker of treatment response
3) Biomarker of target engagement

The only treatment reason to use biomarker or closed-loop is to accelerate dose titration.
How we **titrate dose** (optimize) is the hypothesized **mechanism of action**
Neuromodulation is leading our understanding of normal brain function and pathology.

When characterizing (complex systems) a method to perturb the system is required.
Dose titration based on biomarkers

- Electrodes: electrophysiological biomarkers & electrical stimulation
- "BCI" when there is "intent", or not
Forecasting biomarkers

Mechanism of action

Stimulator

Brain

Behavior

Error

Desired Brain State / Behavior

Sensor

Biomarker

Model of Future Brain State / Behavior

( Current Brain State )
Brain Sensor

Stimulator

Error

Desired Brain State

Mechanism of action

Model of Brain

Behavior

Sensor

Biomarker

Model of Brain: Decoder

Model of Stimulation MoA: I/O
Brain Sensor (Current Brain State)

Stimulator + -

Desired Brain State

Error

Model of Brain

Mechanism of action

Brain

Behavior

Biomarker

Sensor

Software Innovation:
Model of Brain: Decoder
Model of Stimulation MoA: I/O

Hardware Innovation:
Sensor Resolution
Stimulator Resolution

• Faster than changes in Biomarker / Brain State
• Determines rate of models training
Invasive

• Focal
• Chronic: acute mechanisms

Non-invasive

• Not focal
• Out-patient: plastic mechanisms
Invasive

- Focal
- Chronic: acute mechanisms

Non-invasive

- Not focal
- Out-patient: plastic mechanisms

- Model driven design
- Circuit neuromodulation
- Brain-state dependent
- Homeostatic mechanisms
How we **titrate dose** (optimize) is the hypothesized **mechanism of action**
Coupled Neuro-Vascular Hypothesis of Neuromodulation

Cautionary tale: Empowering patients in the loop

Khadka et al. Adaptive current tDCS up to 4 mA. *Brain Stim* 2020

A smart tDCS stimulation that allowed higher current stimulation by 1) **closed-loop** (impedance biomarker) and 2) **open-loop patient control** (“relax” current button)
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Extra Slides
Dose titration is optimization to a goal

When biomarkers are a surrogate to clinical goals
Focal transcranial electrical stimulation
tDCS / tACS

Experimentally-verified Anatomical MRI derived models of current flow

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tDCS / tACS

High Definition tES

Circuit therapeutics

Experimentally-verified Anatomical MRI derived models of current flow

Non-invasive electrical targeting

Circuit therapeutics

Experimentally-verified Anatomical MRI derived models of current flow

• Software steers currents to targeted brain regions
• Single programmable device and head-gear
• Arbitrary / interacting waveforms

Individualized transcranial electrical stimulation
• Different anatomy → Different brain current flow.
• Including for atypical anatomy (neurodegenerative disorders, brain injury), extremes of age…
• When applying the same dose across a population, aggregate response reflect individual variability.

Realistic vOlumetric-Approach-based Simulator for Transcranial electrical stimulation

BRAIN initiative, NIMH. Free (Matlab), Open Source, One command line, validated outcomes.

Huang et al. ROAST -- a fully automated open-source pipeline, bioRxiv 217331, Nov 10, 2017
EEG automatically and instantly “inverted” to optimal HD-tES

- Decades old “reciprocity” hypothesis, but with closed head model
- Activity guided targeting, does not require source localization

Dmochowski J et al. Optimal use of EEG recordings to target active brain areas. *Neuroimage* 2017
Phase II (Harvard/Spaulding) **Fibromyalgia pain**
Daily in-clinic sessions of EEG Guided HD-tDCS, open label
Phase II (Harvard/Spaulding) *Fibromyalgia pain*
Daily in-clinic sessions of EEG Guided HD-tDCS, open label