Conflicts of Interest

- UNC owns IP for my inventions in the field of brain stimulation.
- UNC has determined a “COI with administrative considerations” for our treatment clinical trials.
- I am the founder, chief scientific officer, and majority owner of Pulvinar Neuro LLC (paid as consultant).
- I speak with many companies and have received industry funding from Tal Medical (travel + research + consulting).
- I frequently travel and give presentations. I typically receive reimbursement and a stipend.
- I receive an annual royalty payment for sales of my book “Network Neuroscience” from Elsevier.
Standing on the Shoulders of Giants
Psychiatry Beyond
“Chemical Imbalance in the Brain”
The Brain is an Electrical System.
Brain Rhythm

Alpha Oscillation
Synchronization
NEUROTECHNOLOGY

Synergies with other treatments.
Adaptive, individualized therapies.
Mobile, on-demand diagnosis and treatment.
FIGURE 1. Effect of Active and Sham Transcranial Direct-Current Stimulation (tDCS) on the Severity of Auditory Verbal Hallucinations.

The graph illustrates the significant interaction between the mean percentage change in Auditory Hallucination Rating Scale (AHRSS) score in the two groups across the four assessments ($F=10.97$, $df=3$, 84, $p<0.0001$). Post hoc analyses showed significant differences between groups at each postbaseline assessment: after tDCS, $t=4.45$, $p<0.001$; 1 month after treatment, $t=4.48$, $p<0.001$; 3 months after treatment, $t=4.58$, $p<0.001$. Error bars indicate standard error.

Brunelin et al. 2012

Frohlich et al. 2015
Sellers et al. 2015
Lesson #1

Do not skip measuring brain activity (EEG, fMRI, etc.). #BeDifferent
VERTICAL INTEGRATION

Patients

Clinical Trials

Brain Stimulation, Human Neurophysiology

In vivo (Animal) Electrophysiology

In vitro (Animal) Electrophysiology

Computer Simulations

Model Systems

COMPLEXITY

TRACTABILITY
Lesson #2

Leverage the tools of (network) neuroscience.

#Collaboration
TRANSCRANIAL CURRENT STIMULATION
STUDY DESIGN

Behavioral Target

Network Target

Target Engagement
Lesson #3

Make sure you know your target and have a plan how to engage it.

#RationalDesign
TARGET ENGAGEMENT

How do we best engage a network target?

We need to understand what the effect of stimulation is on the brain in terms of neurophysiology.
Using Transcranial Alternating Current Stimulation (tACS) to Improve Romantic Relationships Can Be a Promising Approach

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³School of Foreign Languages, Anhui Jianzhu University, Hefei, China
⁴Department of Mechanical and Automation Engineering, The Chinese University of Hong Kong, Hong Kong, China
OUTLINE

1. Cellular Effects
2. Spatial Targeting
3. Targeting Network Dynamics
ELECTRIC FIELDS

How do electric fields change electric signaling in neurons?
"Anodal"
Depolarized Soma
Hyperpolarized Dendrite

"Cathodal"
Hyperpolarized Soma
Depolarized Dendrite
NEURONAL MORPHOLOGY AND STATE

Change in somatic membrane voltage:

- Increases with cable length.
- Decreases with membrane conductance.
- Increases with cable diameter.

A vs. B

Radmann et al. 2009
Change in somatic membrane voltage can be modeled as a sub-threshold somatic current injection.
Lesson #4

tDCS/tACS cause small changes in neuronal membrane voltage. #synergy #EndogenousBrainActivity
Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review

Popular brain stimulation methods can’t trigger neuronal firing, a study in cadavers suggests. MIHÁLY VÖRÖSLAKOS/UNIVERSITY OF SZEGET

Cadaver study casts doubts on how zapping brain may boost mood, relieve pain

By Emily Underwood  |  Apr. 20, 2016 , 3:00 AM

Earlier this month, György Buzsáki of New York University (NYU) in New York City showed a slide that sent a murmur through an audience in the Grand Ballroom of New York’s Midtown Hilton during the annual meeting of the Cognitive Neuroscience Society. It wasn’t just the grisly image of a human cadaver with more than 200 electrodes inserted into its brain that set people whispering; it was what those electrodes detected—or rather, what they failed to detect.
The cadaver research “should make the crowd nervous that favors tDCS and tACS,” says David Poeppel, a neuroscientist and psychologist at NYU.

Marom Bikson, a biomedical engineer at The City College of New York in New York City who uses computer models and slices of rat brain to study the mechanisms of tDCS and tACS, says that many in the field already accepted that the 1 or 2 milliamps the methods use don’t directly trigger firing.

The tDCS field is “a sea of bullshit and bad science—and I say that as someone who has contributed some of the papers that have put gas in the tDCS tank,” says neuroscientist Vincent Walsh of University College London. “It really needs to be put under scrutiny like this.”
TMS-tDCS-EEG study

TMS (left precentral gyrus) using Neuronavigation

2 mA tDCS (M1-SO montage)
  Anode Cathode Sham

High-Density EEG with Digitizer
Replication (Motor-Evoked Potential)

Ahn et al., in preparation.
Grand-averaged TMS-evoked potential (TEP)
<table>
<thead>
<tr>
<th>Tissue</th>
<th>Resistivity [Ohm cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper</td>
<td>2e-6</td>
</tr>
<tr>
<td>CSF</td>
<td>64</td>
</tr>
<tr>
<td>Cortex</td>
<td>350</td>
</tr>
<tr>
<td>White Matter</td>
<td>650</td>
</tr>
<tr>
<td>Bone</td>
<td>8,000-16,000</td>
</tr>
</tbody>
</table>
IMPLEMENTATION

• MR Scan
• Tissue segmentation
• Numerical solution (e.g. finite elements).

1. Develop your own code
2. Collaborate
3. Buy tool / use free tool
Lesson #5

MR scan + Segmentation + EF modeling = Spatial Targeting

#KnowYour3D
#HowGoodisHD
MODELING DYNAMICS

- Brain Areas
- Networks
- Neurons and Glial Cells
- Synapses
- Molecules

Spatial Scale

cm ($10^{-2}$m)

Macroscopic

Mesoscopic

Microscopic

nm ($10^{-9}$m)

Frohlich 2014
Caution: Most tACS literature refers to the peak-to-peak amplitude as amplitude.
1. Raw trace.


1. Raw trace.


1. Raw trace.
Lesson #6

Brain rhythms effectively targeted by rhythmic brain stimulation

#MiddleSchoolMath
TARGETING BRAIN NETWORK DYNAMICS

Transcranial Alternating Current Stimulation (tACS)


Berger 1929
SPIKING NEURAL MODEL (NETWORK)
SPATIO-TEMPORAL DYNAMICS

Ali et al. 2013
STIMULATION PHASE

Ali et al. 2013
HOTSPOTS

T = 0 msec
4 Hotspots

T = 30 msec
3 Hotspots

T = 90 msec
1 Hotspot

T = 120 msec
2 Hotspots

T = 150 msec
1 Hotspot

T = 180 msec
4 Hotspots

T = 210 msec
4 Hotspots

T = 310 msec
10 Hotspots

Ali et al. 2013
NETWORK-LEVEL MECHANISM

Ali et al. 2013
CELLULAR-LEVEL MECHANISM

Ali et al. 2013
TARGETING A SUBPOPULATION

Ali et al. 2013
NETWORK RESONANCE

![Graph showing network resonance](image)

**Stimulation Amplitude [pA]**
- 13
- 9
- 5
- 1

**Stimulation Frequency [Hz]**
- 0
- 0.5
- 1
- 1.5
- 2
- 2.5
- 3
- 3.5
- 4
- 4.5
- 5
- 5.5
- 6

Ali et al. 2013
PHASE SLIPPING

Ali et al. 2013
INTERACTING NETWORKS

G[LRP] = 0

G[LRP] = 0.06

Kutchko and Frohlich 2013
MULTISTABILITY

“Rapid Fire”
Delay = 10 msec; P(local) = 0.95; G(LRP) = 0.03

“Slow Propagating”
Delay = 50 msec; P(local) = 0.97; G(LRP) = 0.015

“Spiral Waves”
Delay = 5 msec; P(local) = 0.99; G(LRP) = 0.12

Kutchko and Frohlich 2013
STATE SWITCHING BY tACS

Kutchko and Frohlich 2013
Lesson #7

Complexity of brain dynamics requires computer simulations to understand target engagement.

#MultiStability
TARGET: ALPHA OSCILLATIONS

- “Offline” state, long-range functional connectivity, gating.

- Neurofeedback, rTMS (10 Hz), tACS, others...
“increased alpha power during creative ideation is among the most consistent findings in neuroscientific research on creativity” (Fink and Benedek, 2010)
Blinding was successful (p > 0.2).

10 Hz tACS significantly enhances creativity as measured by the Torrance Test of Creative Thinking (7.45 % ± 3.11 % S.E.M.; F_{1,16} = 5.14, p = 0.036).

No enhancement with 40Hz-tACS.
OSCILLATION ENHANCEMENT

Enhancement of Power at Endogenous Frequency

Power [µV²/Hz]

Frequency [Hz]

Time [s]

During Stimulation

After Stimulation
IMPROVING MEMORY CONSOLIDATION

Lustenberger et al. (2015)
TARGET ENGAGEMENT
Lesson #8

Individualize with feedback stimulation to enhance target engagement.

#OMGWasThatASpindle
SUMMARY: TARGETING NETWORK DYNAMICS

- Oscillations represent fundamental activity structure.
- tACS ideal to target cortical oscillations.
- Endogenous network dynamics represent oscillator to be modulated by weak periodic perturbations.
- Arnold Tongue: Necessity of individualizing stimulation frequency?
- Multistable dynamics: State-dependent stimulation effects.

Join the Flavio Network to learn more about the brain. Understand how networks and ecosystems in our body shape who we are, how we feel, and how we act. Change your life by joining a leading neuroscientist and innovator to Learn. Grow. Transform.

JOIN NOW
Neurons, Synapses, and Circuits.
Measuring, Perturbing, and Analyzing Brain Networks
Cortical Oscillations
Network Disorders
Toolboxes
Thank you for your attention.

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