THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

UNC SCHOOL OF MEDICINE

Mechanisms of TES: Neurophysiology

Flavio Frohlich

University of North Carolina - Chapel Hill
Department of Psychiatry
Department of Cell Biology and Physiology
Department of Biomedical Engineering
Department of Neurology
Neuroscience Center

North Carolina State University
Department of Electrical and Computer Engineering

University of Bern
Department of Neurology

www.networkneuroscientist.org

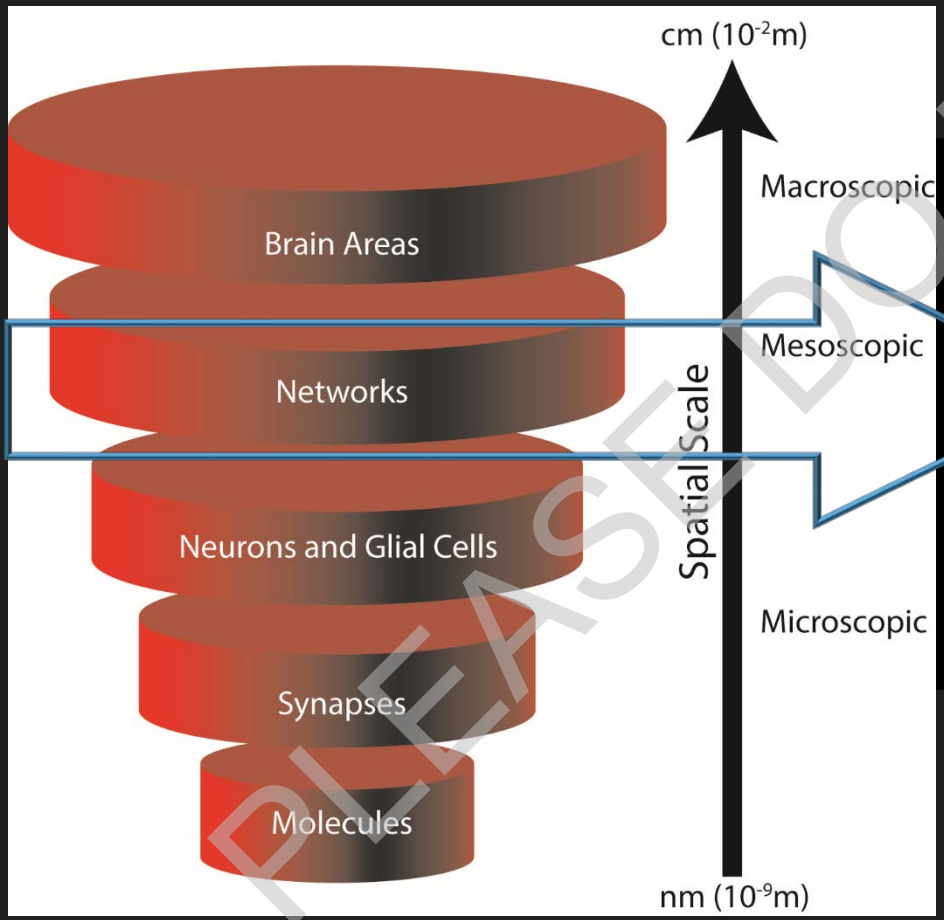
@FrohlichLab

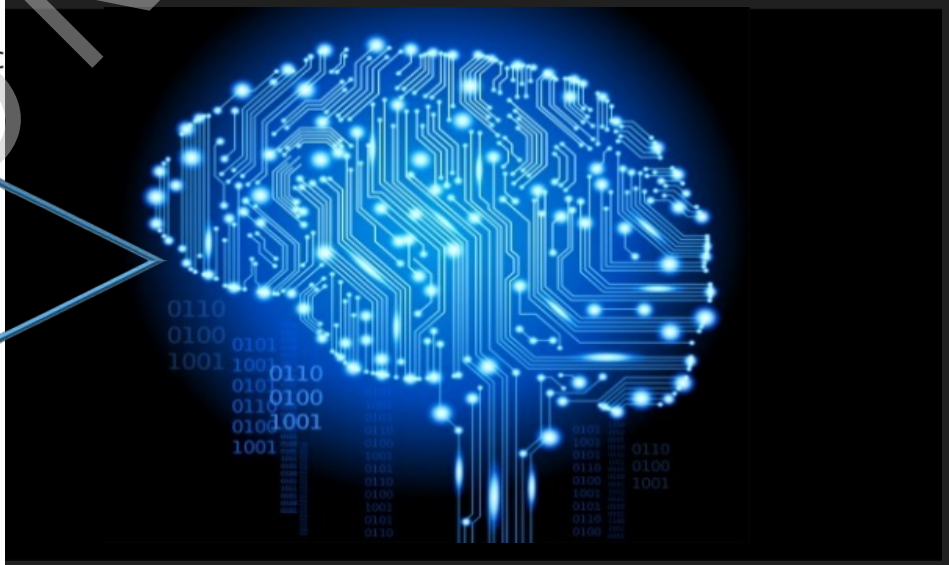
Conflicts of Interest

- 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

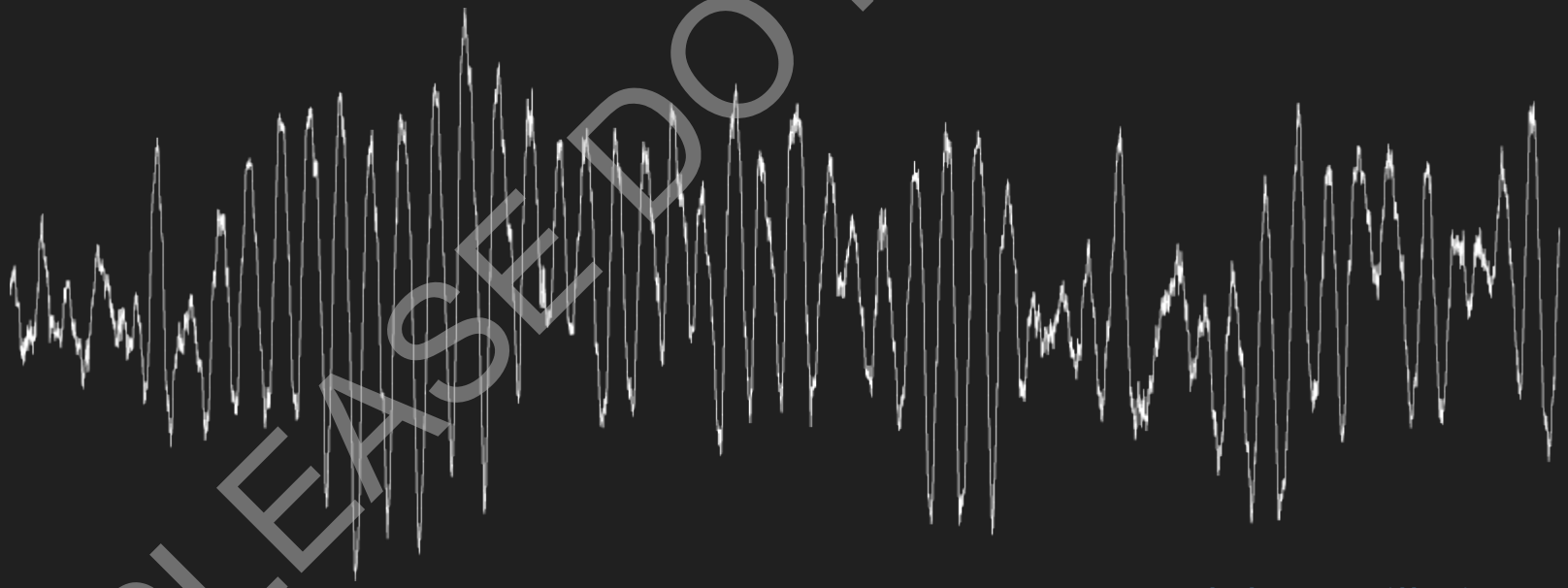
Psychiatry Beyond "Chemical Imbalance in the Brain"



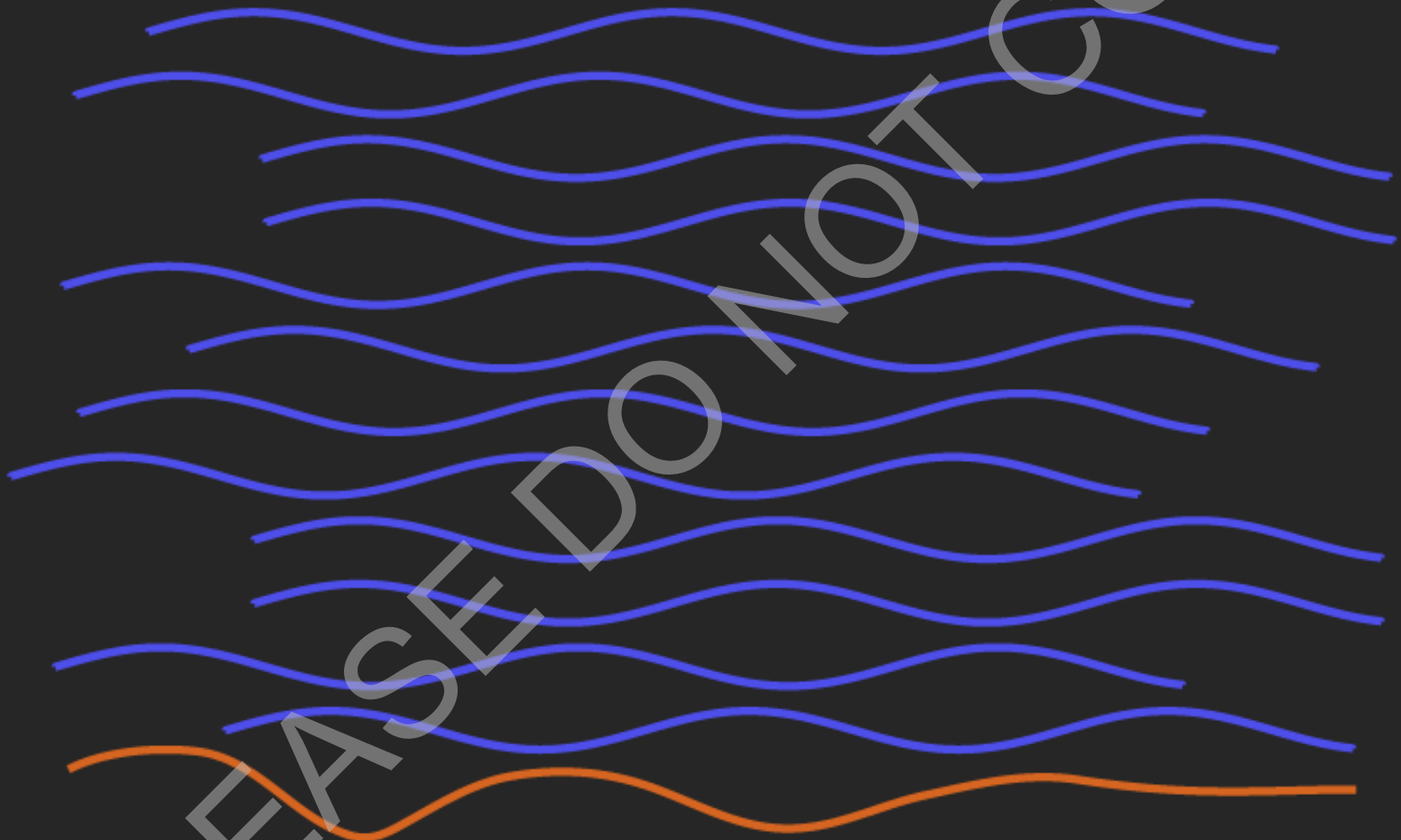


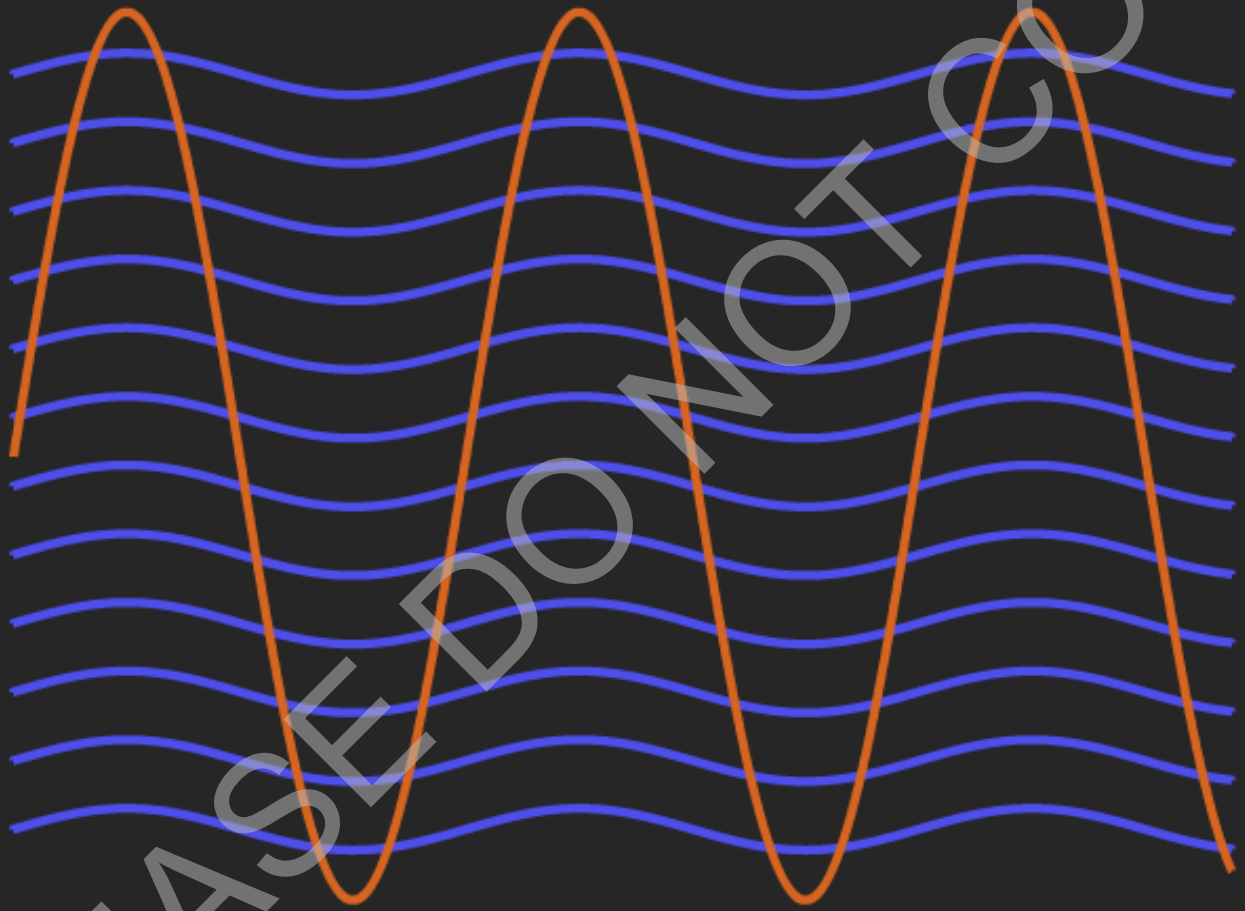
The Brain is an Electrical System.

Brain Rhythm

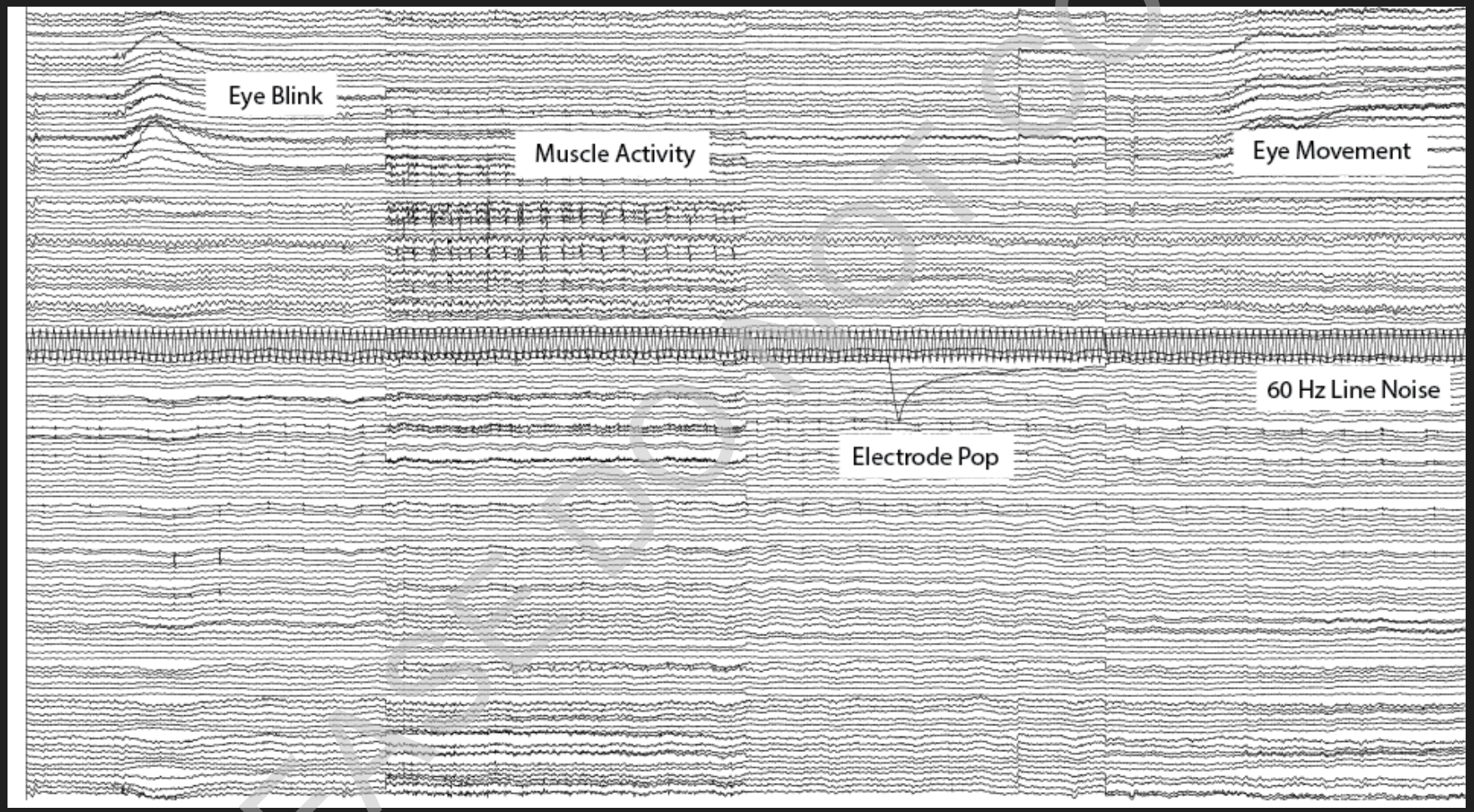


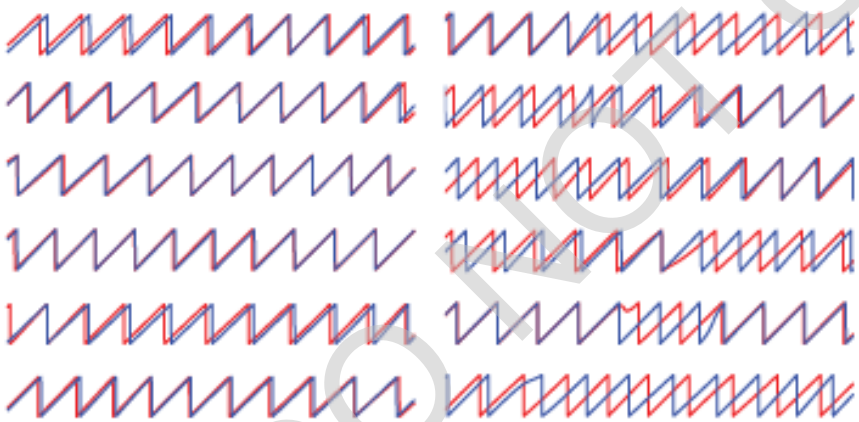
Alpha Oscillation



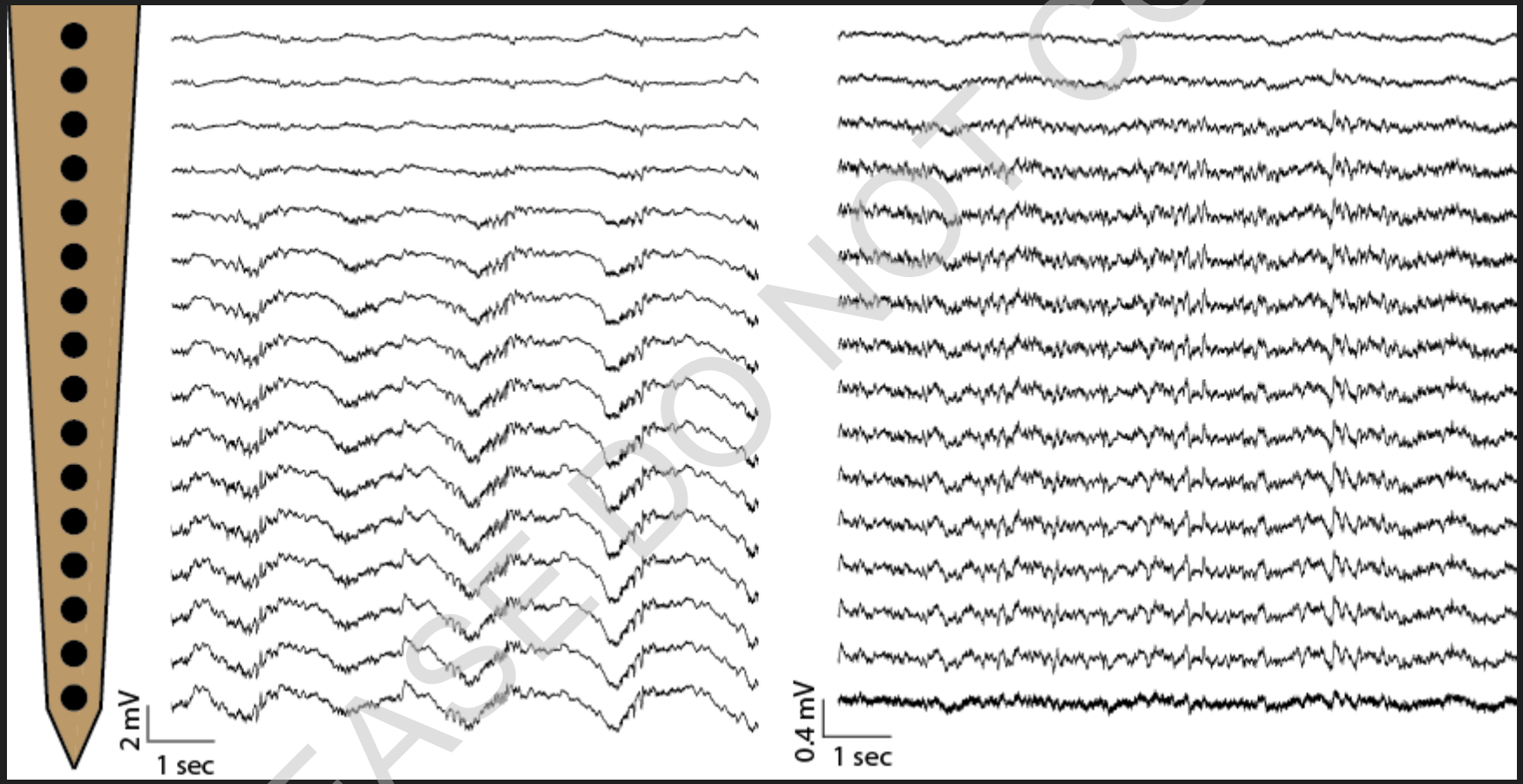


Synchronization





Sellers et al (2016)



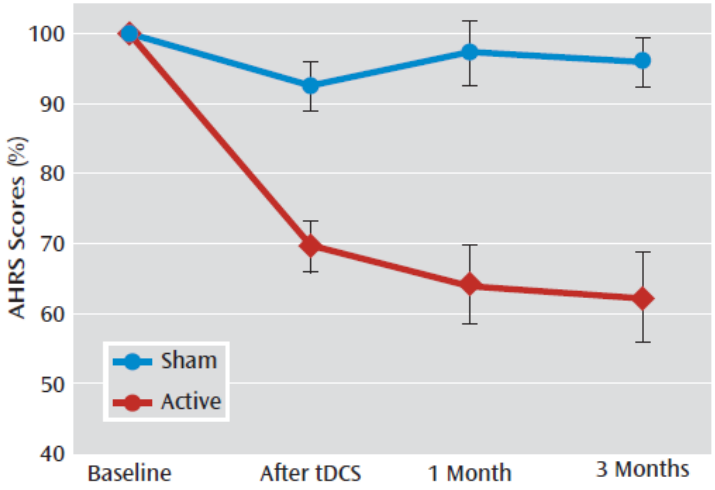
NEUROTECHNOLOGY

Synergies with other treatments.

Adaptive, individualized therapies.

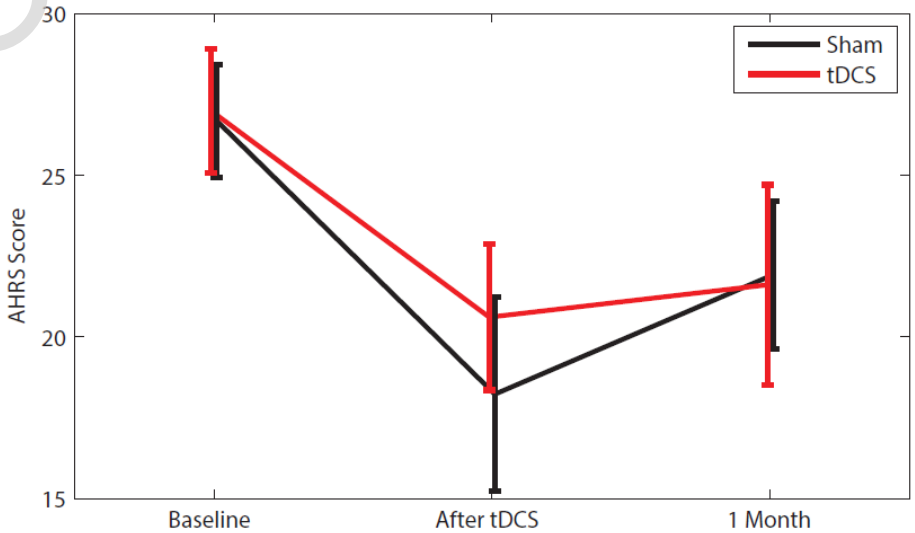
Mobile, on-demand diagnosis and treatment.

FIGURE 1. Effect of Active and Sham Transcranial Direct-Current Stimulation (tDCS) on the Severity of Auditory Verbal Hallucinations[a]

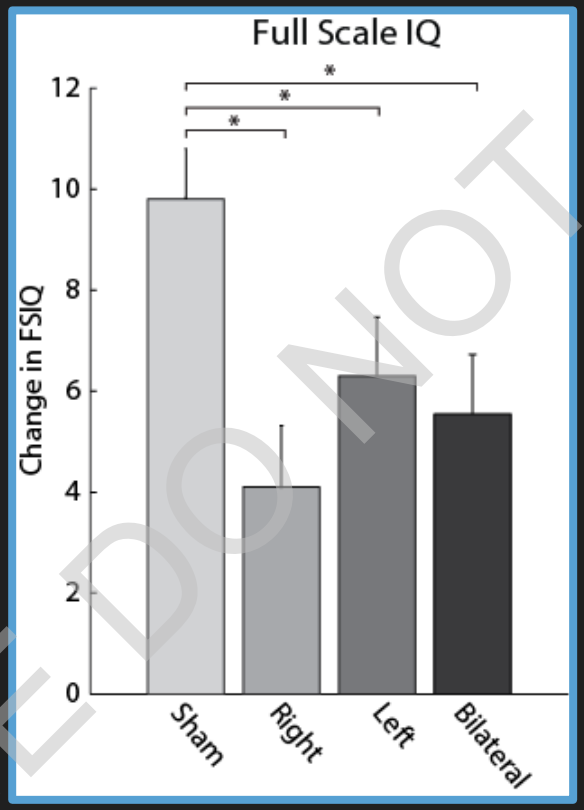


[a] The graph illustrates the significant interaction between the mean percentage change in Auditory Hallucination Rating Scale (AHRS) score in the two groups across the four assessments ($F=10.97$, $df=3, 84$, $p<0.0001$). Post hoc analyses showed significant differences between groups at each postbaseline 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

Model Systems

Clinical Trials

Brain Stimulation,
Human Neurophysiology

In vivo (Animal)
Electrophysiology

In vitro (Animal)
Electrophysiology

Computer Simulations

Lesson #2

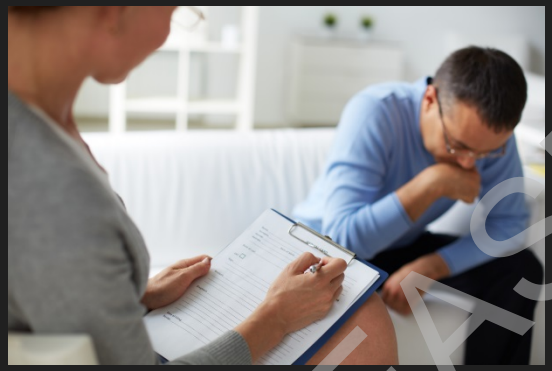
Leverage the tools of (network) neuroscience.
#Collaboration

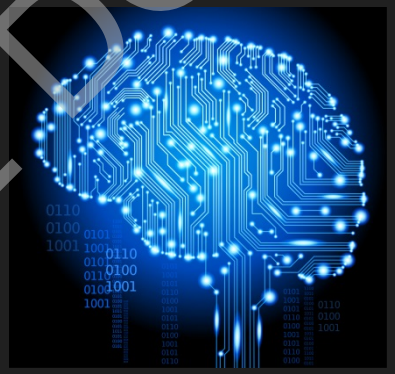
TRANSCRANIAL CURRENT STIMULATION STUDY DESIGN

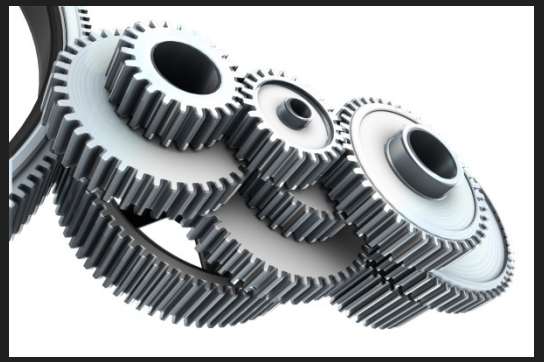
Behavioral Target

Network Target

Target Engagement





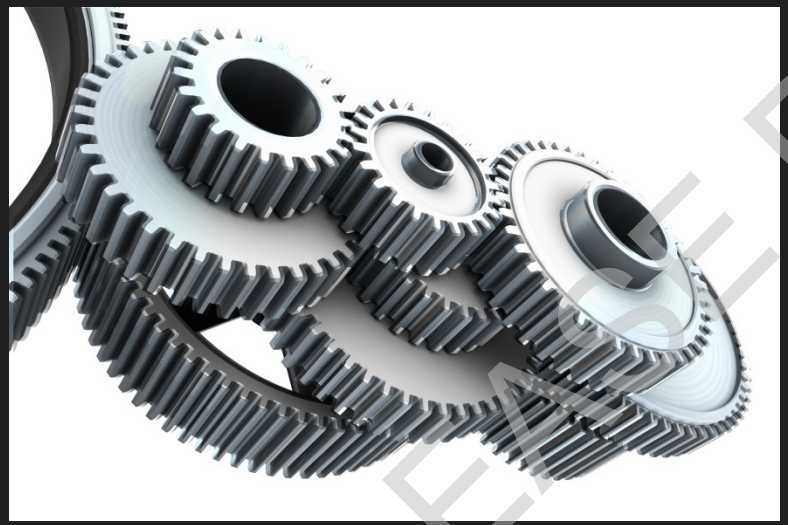


Lesson #3

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*.

#target #**targetengagement** #engaged #isaidyes @Target – at Target

REVIEWED BY

Juan Hou
Anhui University, China

Lumei Tian
Shandong Normal University, China

Xiuyan Guo
East China Normal University, China

The editor and reviewers' affiliations are the latest provided on their Loop research profiles and may not reflect their situation at the time of review.

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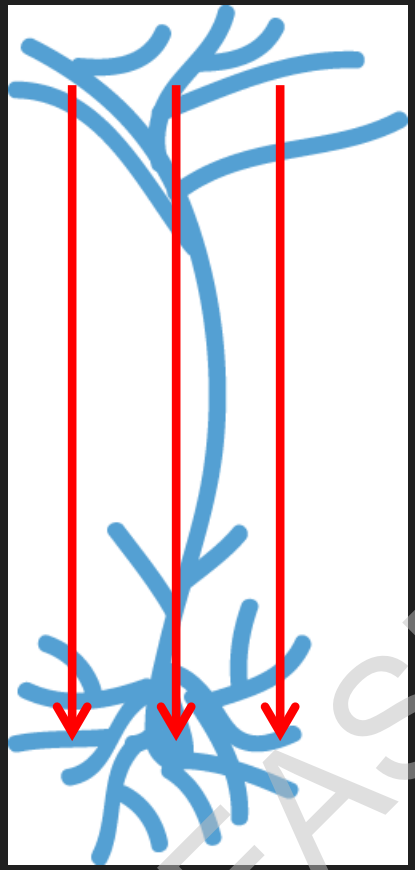
Shen Liu[1], Ru Ma[2], Xiaoming Liu[1,3], Chong Zhang[4], Yijun Chen[2], Chenggong Jin[2], Hangwei Wang[2], Jiangtian Cui[5] and Xiaochu Zhang[1,2,6,7*]

[1]School of Humanities and Social Science, University of Science and Technology of China, Hefei, China
[2]Hefei National Laboratory for Physical Sciences at the Microscale and School of Life Sciences, University of Science and Technology of China, Hefei, China
[3]School of Foreign Languages, Anhui Jianzhu University, Hefei, China
[4]Department of Mechanical and Automation Engineering, The Chinese University of Hong Kong, Hong Kong, China

OUTLINE

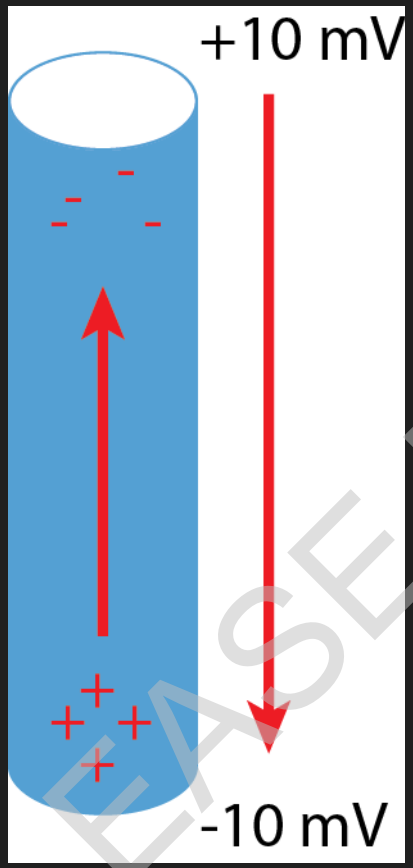
1. Cellular Effects
2. Spatial Targeting
3. Targeting Network Dynamics

ELECTRIC FIELDS

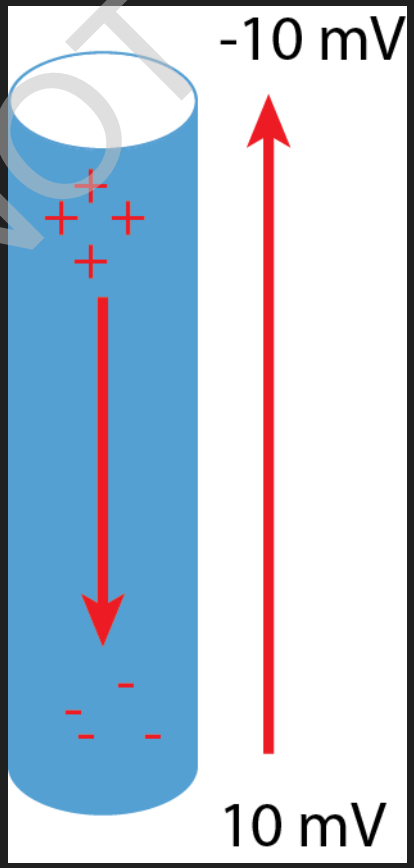


How do electric fields change electric signaling in neurons?

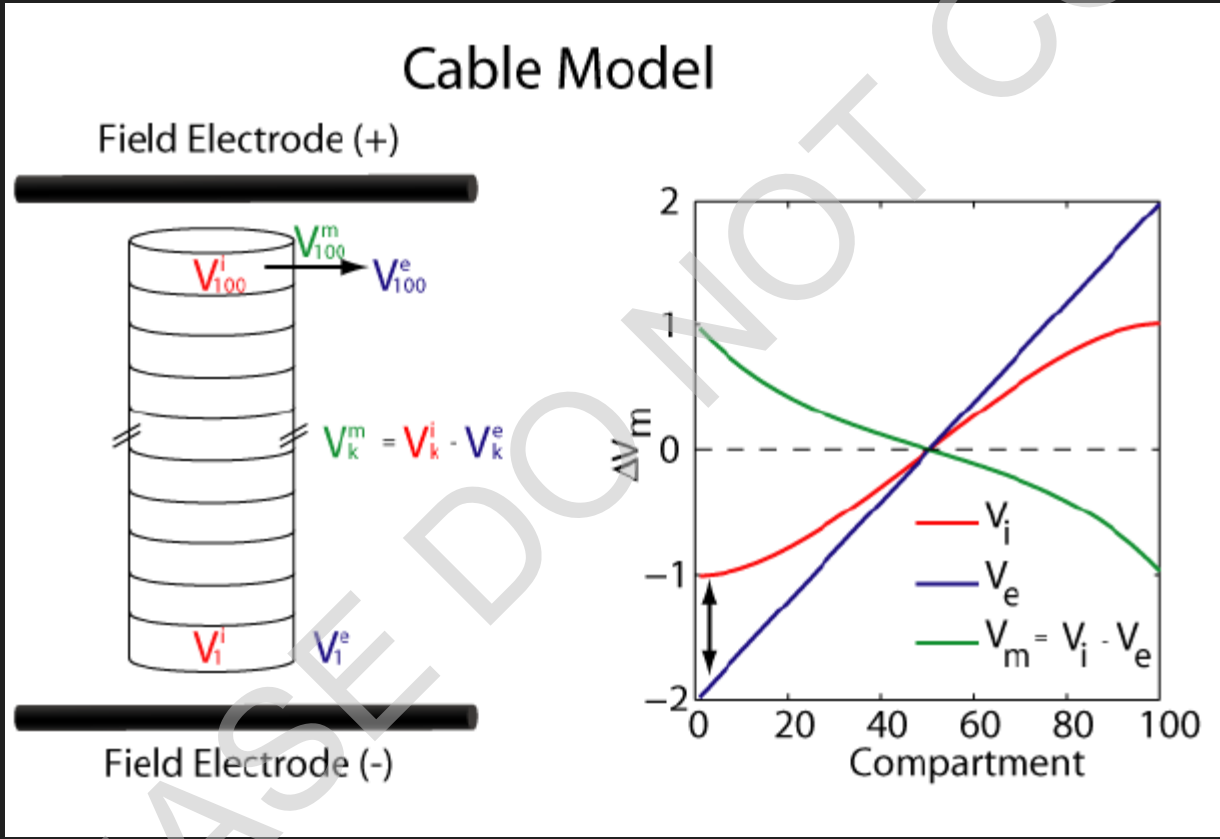
"Anodal"
Depolarized Soma
Hyperpolarized Dendrite



"Cathodal"
Hyperpolarized Soma
Depolarized Dendrite



CABLE EQUATION

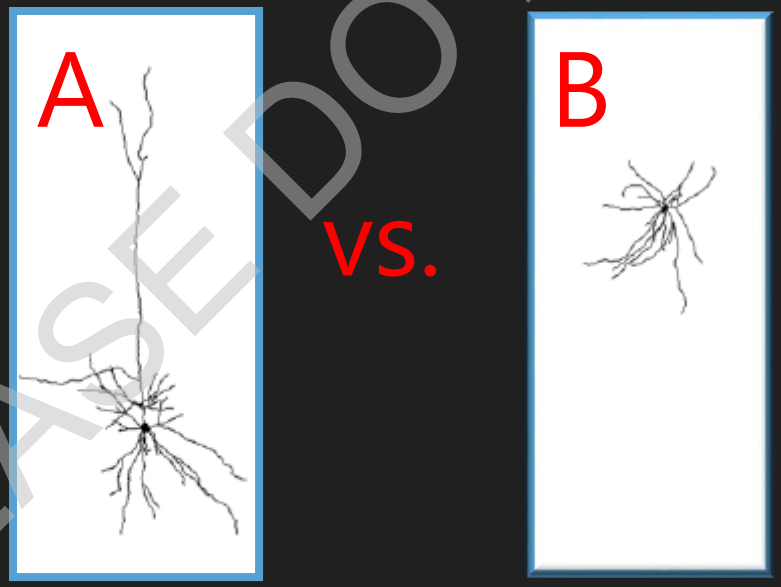


Frohlich and McCormick. 2010

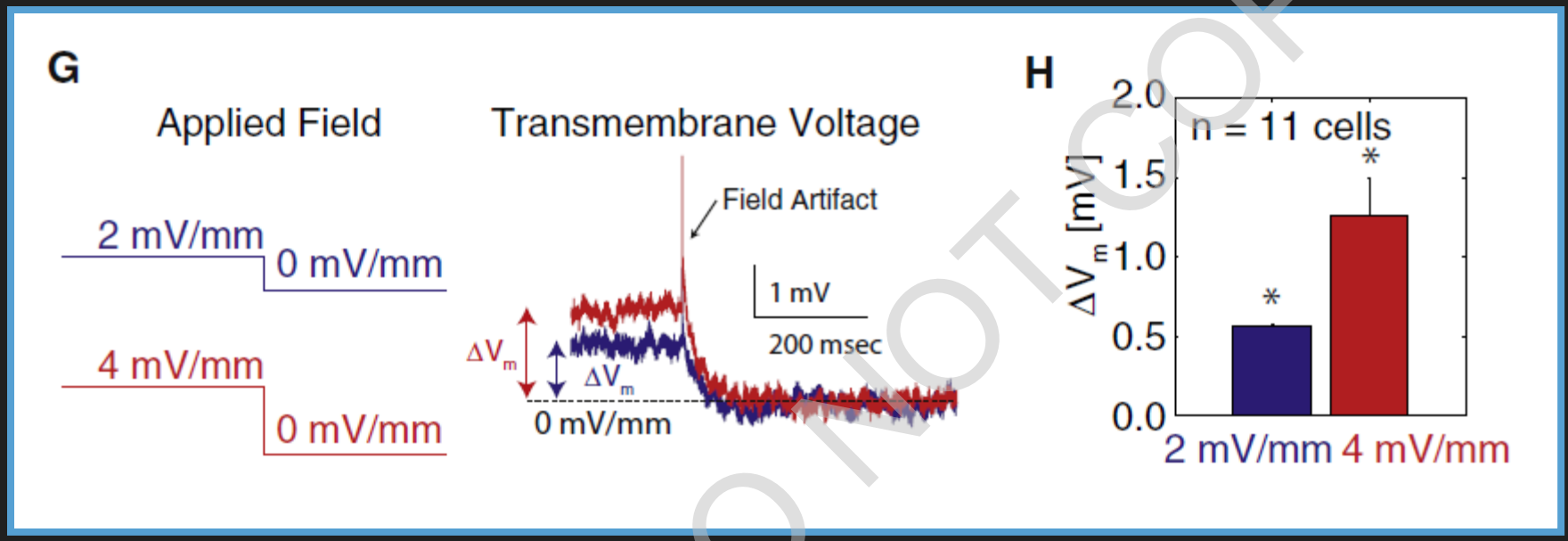
NEURONAL MORPHOLOGY AND STATE

Change in somatic membrane voltage:

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



Radmann et al. 2009



Change in somatic membrane voltage can be modeled as a sub-threshold somatic current injection.

Frohlich and McCormick. 2010

Lesson #4

tDCS/tACS cause small changes in neuronal membrane voltage. #synergy #EndogenousBrainActivity

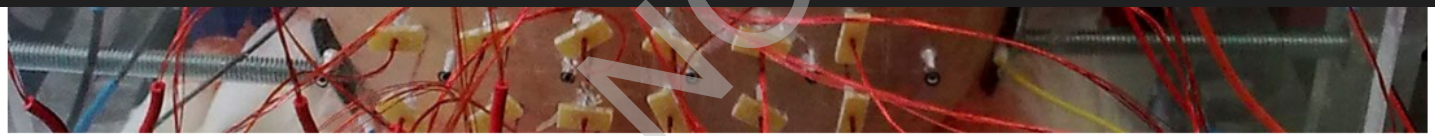
Neuropsychologia
Volume 66, January 2015, Pages 213-236

Reviews and perspectives

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

Jared Cooney Horvath, Jason D. Forte, Olivia Carter

Show more



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

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.

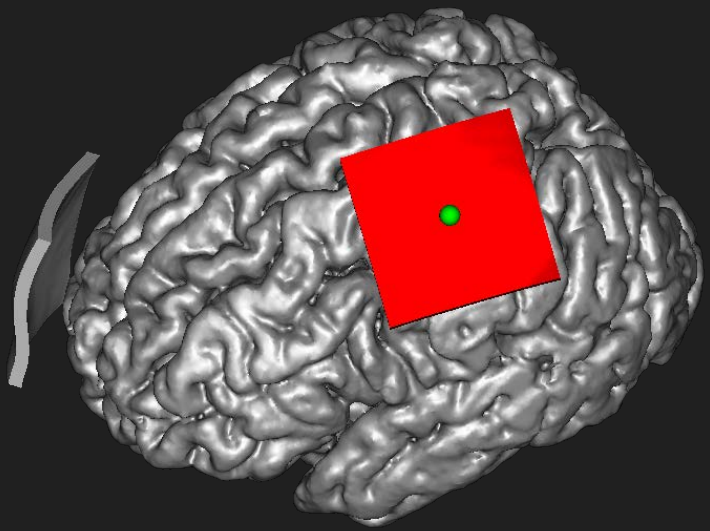
The tDCS field is “a sea of bullshit and bad science—and I say that as someone who has contributed some of the papers that have put gas in the tDCS tank,” says neuroscientist Vincent Walsh of University College London. “It really needs to be put under scrutiny like this.”

TMS-tDCS-EEG study

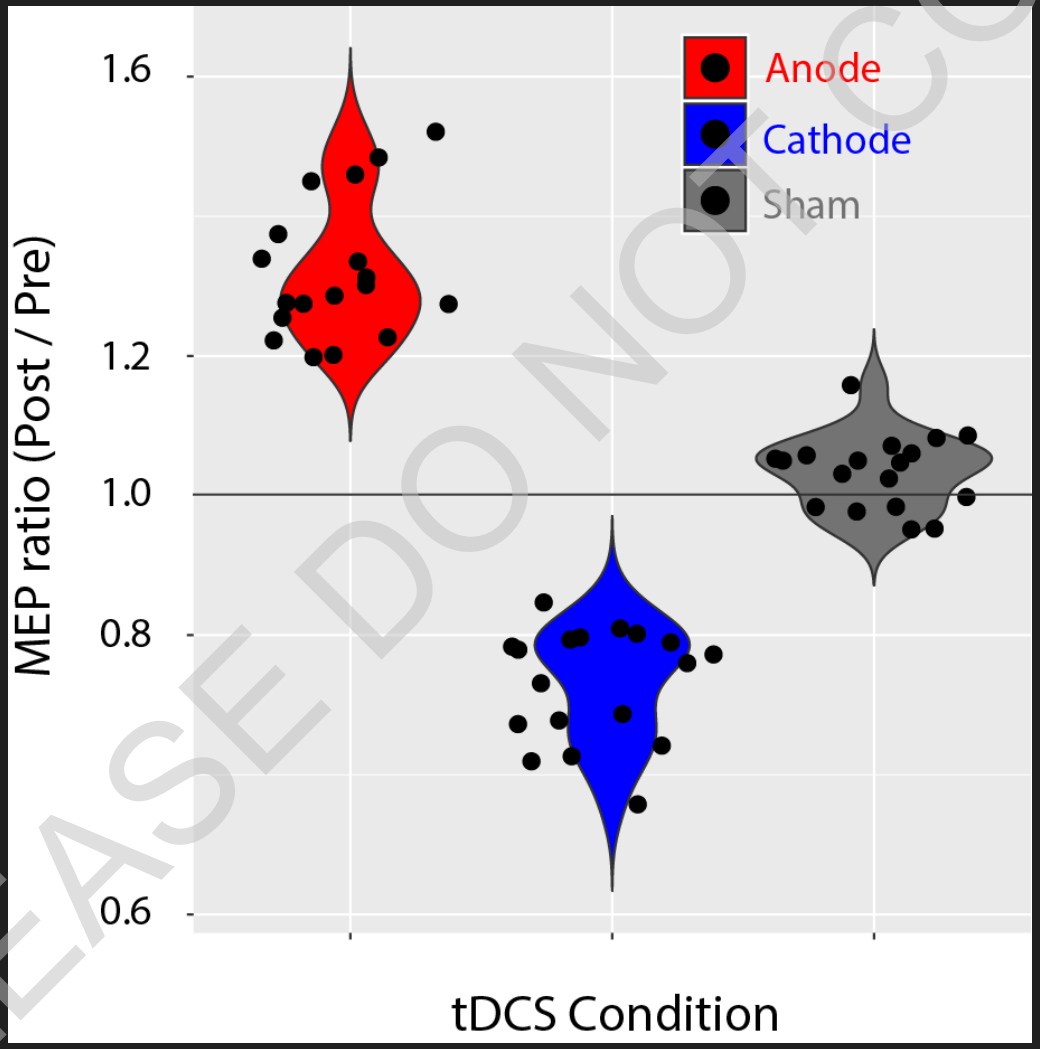
High-Density EEG with Digitizer

TMS (left precentral gyrus)
using Neuronavigation

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

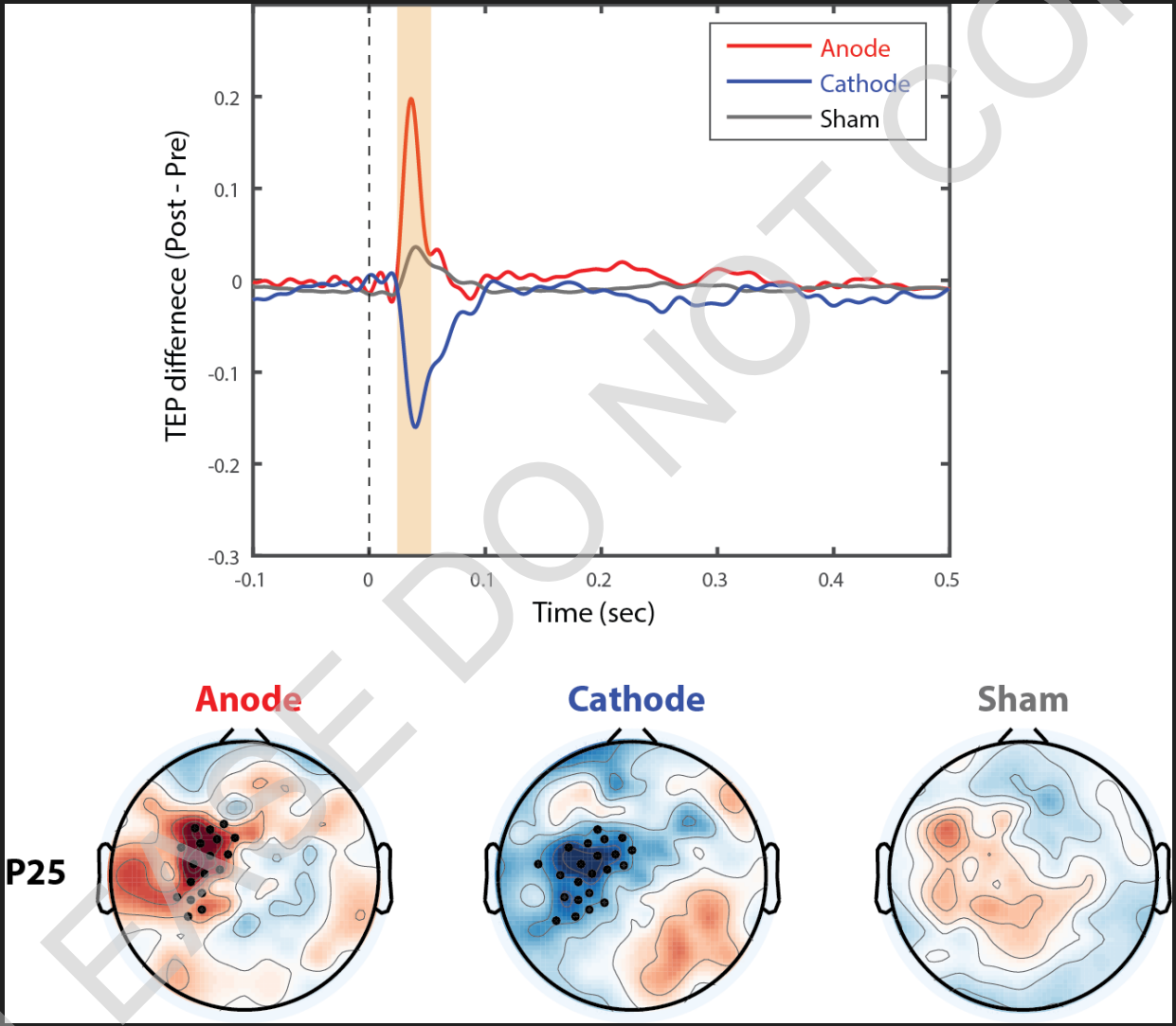


Replication (Motor-Evoked Potential)



Ahn et al., in preparation.

Grand-averaged TMS-evoked potential (TEP)



Ahn et al., in preparation.

SPATIAL TARGETING

Tissue	Resistivity [Ohm cm]
Copper	2e-6
CSF	64
Cortex	350
White Matter	650
Bone	8,000-16,000

IMPLEMENTATION

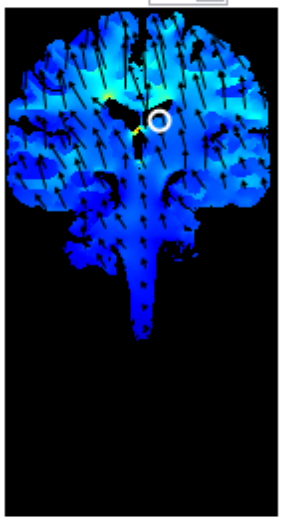
- MR Scan
- Tissue segmentation
- Numerical solution (e.g. finite elements).

1. Develop you own code
2. Collaborate
3. Buy tool / use free tool

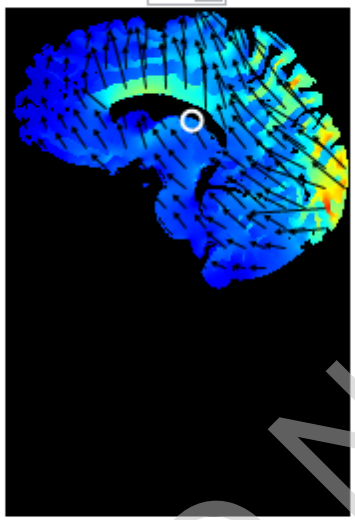
Selected Slice Position: {78,94,57}
Selected MNI Position: {10,-19,21}

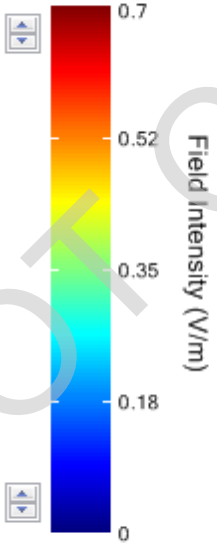
Selected Field Intensity: 0.18 V/m

Coronal Slice: 94

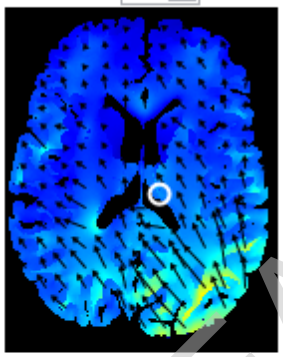


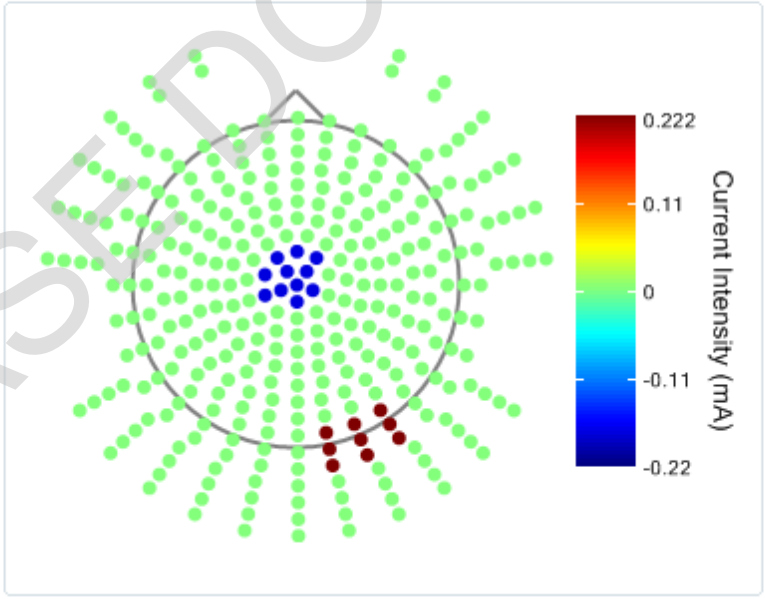
Sagittal Slice: 78





Axial Slice: 57





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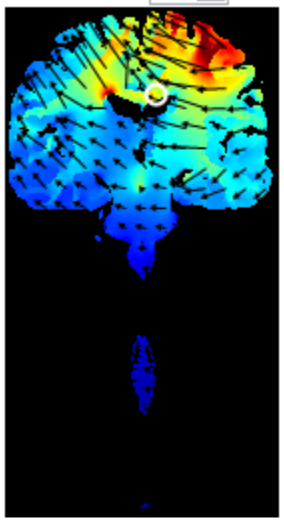
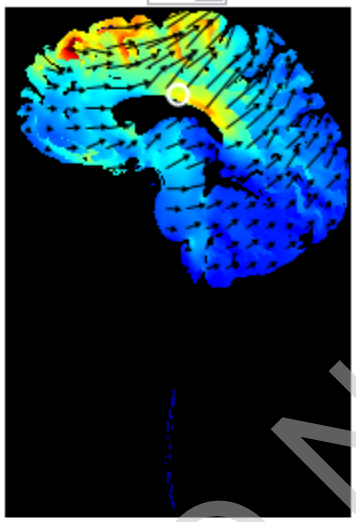
Selected MNI Position: {7,-8,30}

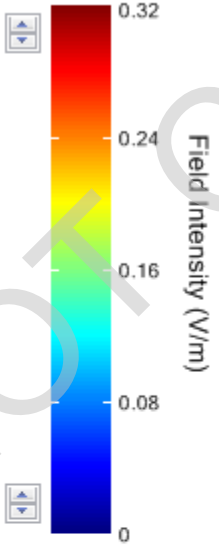
Selected Field Intensity: 0.19 V/m

Coronal Slice: 87

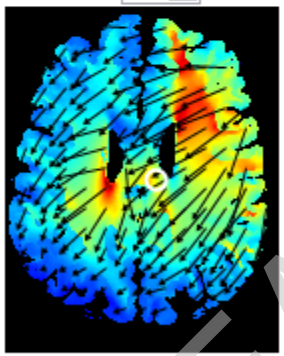


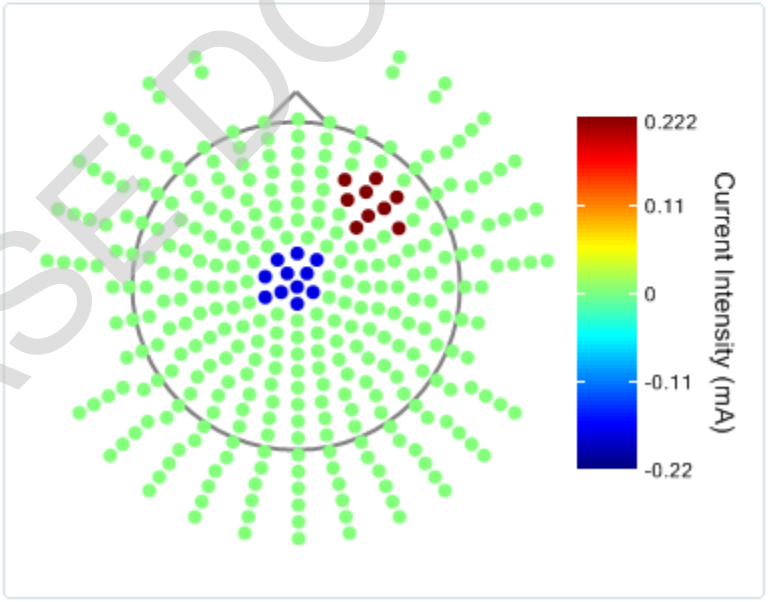
Sagittal Slice: 76

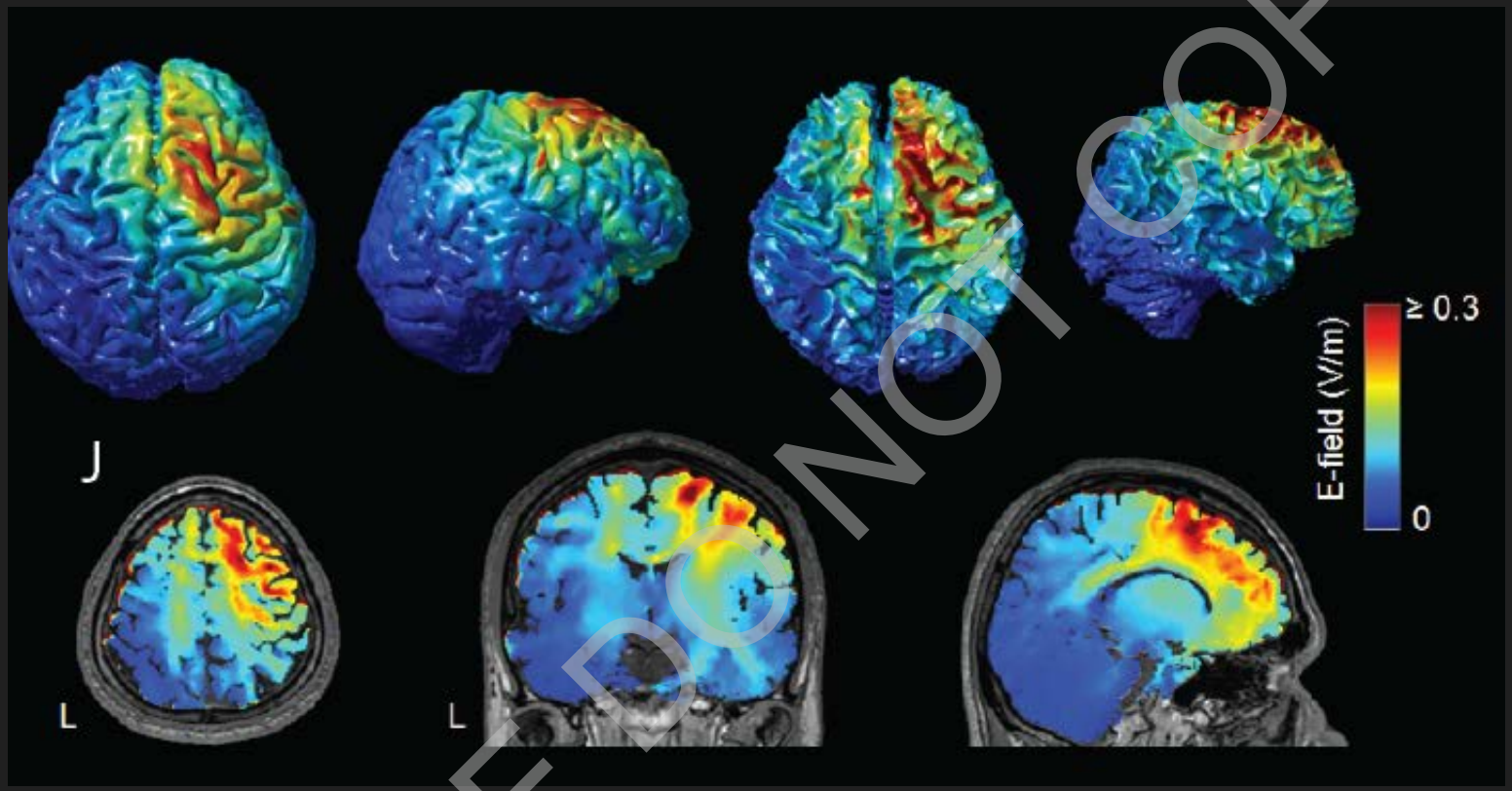




Axial Slice: 44







Modeling performed by Angel Peterchev
Sellers et al 2015

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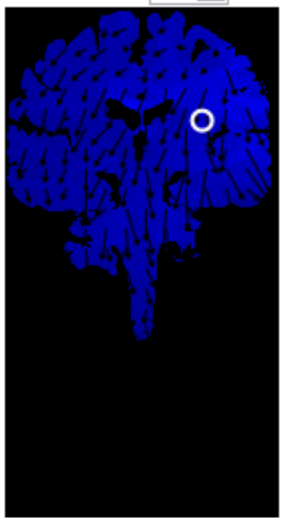
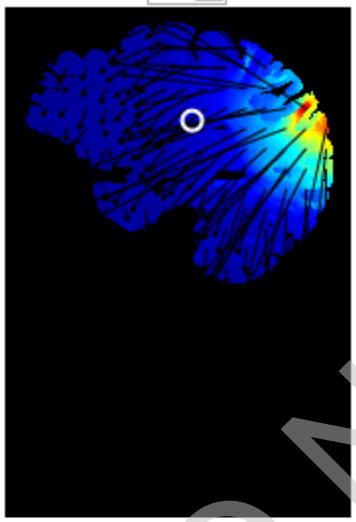
Selected MNI Position: {31,-18,20}

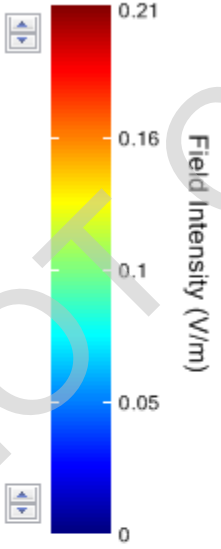
Selected Field Intensity: 0.01 V/m

Coronal Slice: 94

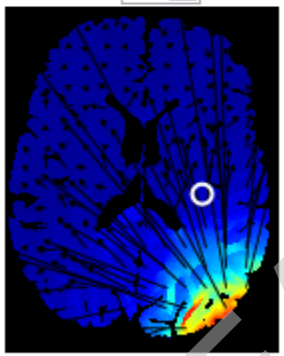


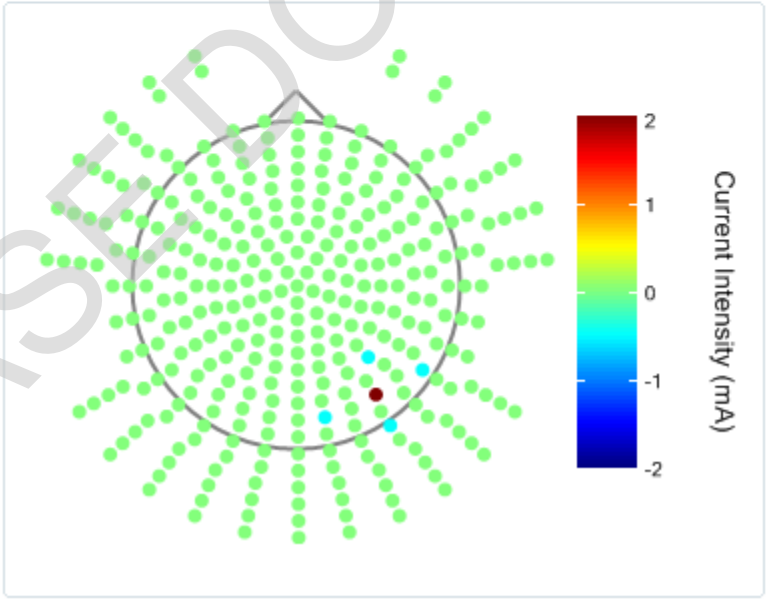
Sagittal Slice: 99





Axial Slice: 57





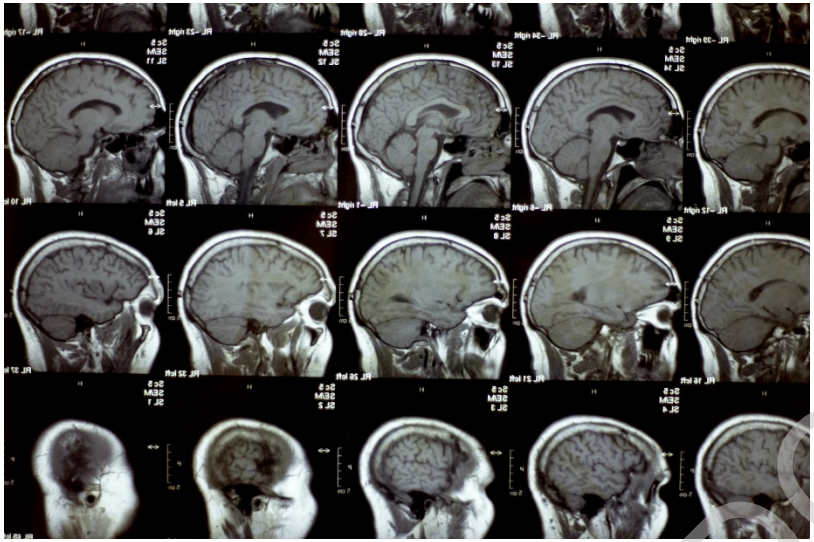
Lesson #5

MR scan + Segmentation + EF modeling = Spatial Targeting

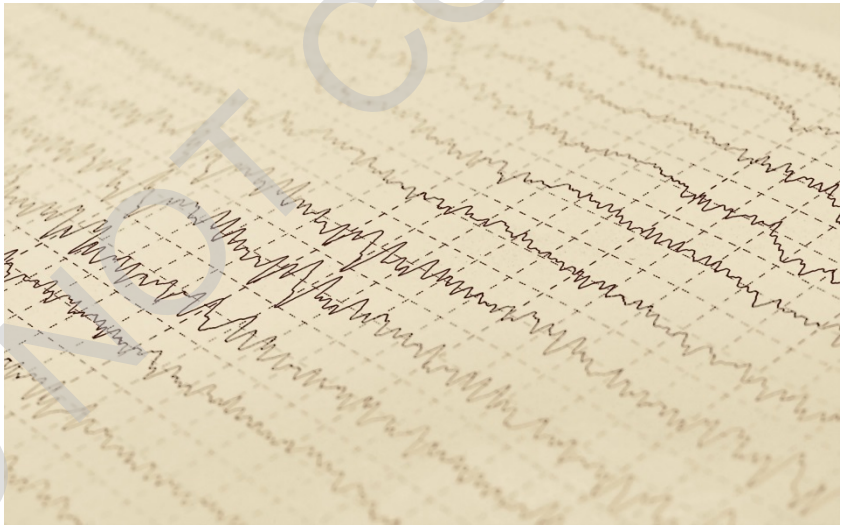
#KnowYour3D

#HowGoodisHD

STRUCTURE

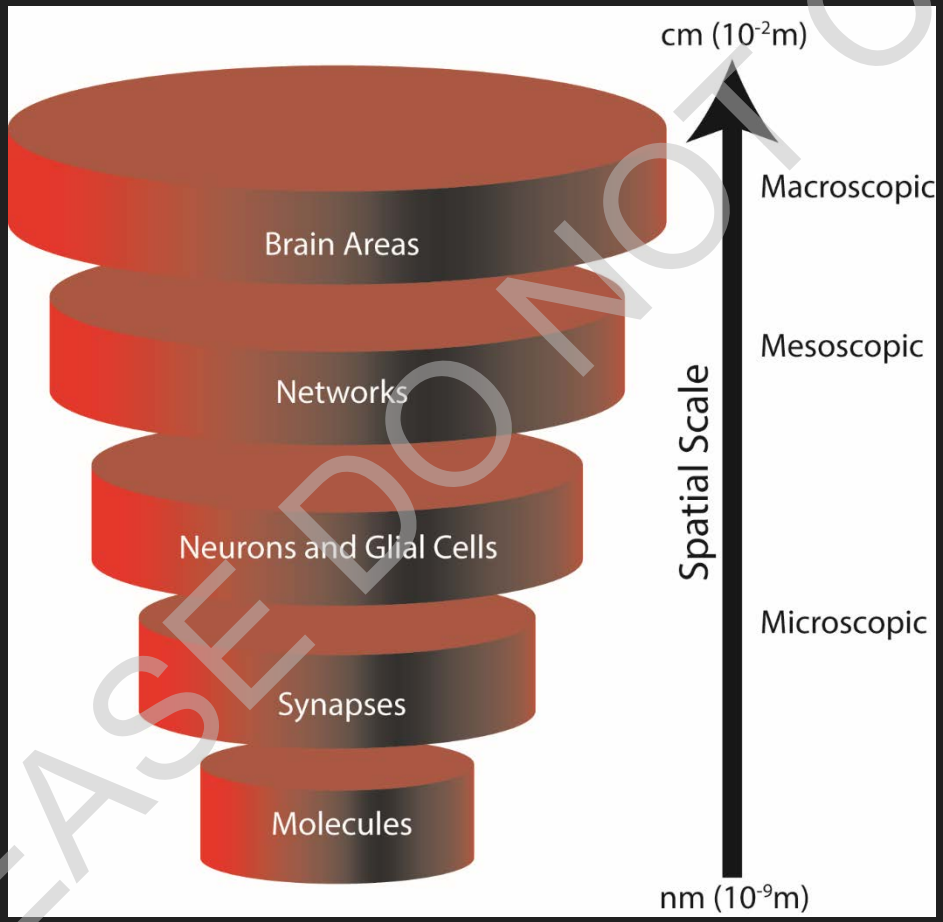


DYNAMICS



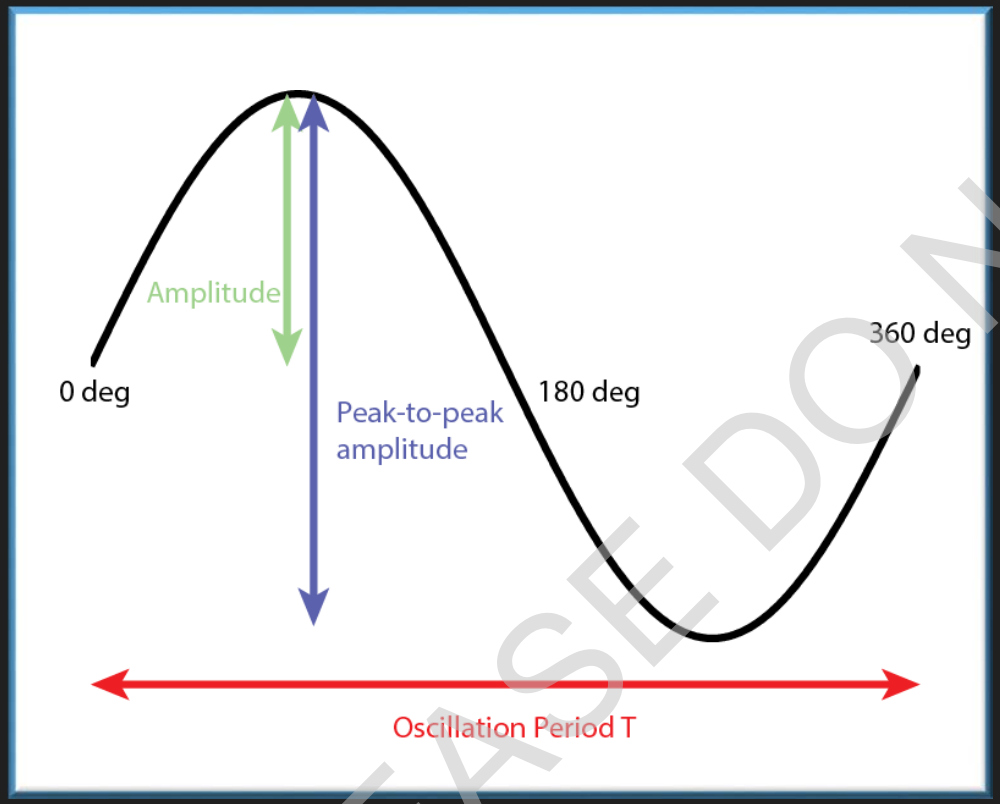
BEHAVIOR

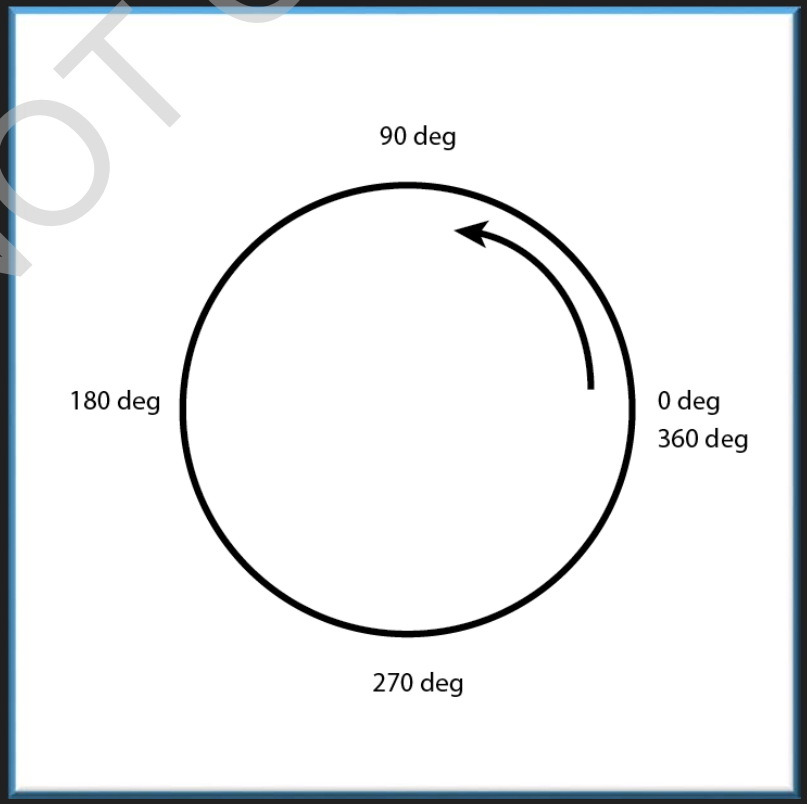
MODELING DYNAMICS



Frohlich 2014

OSCILLATIONS





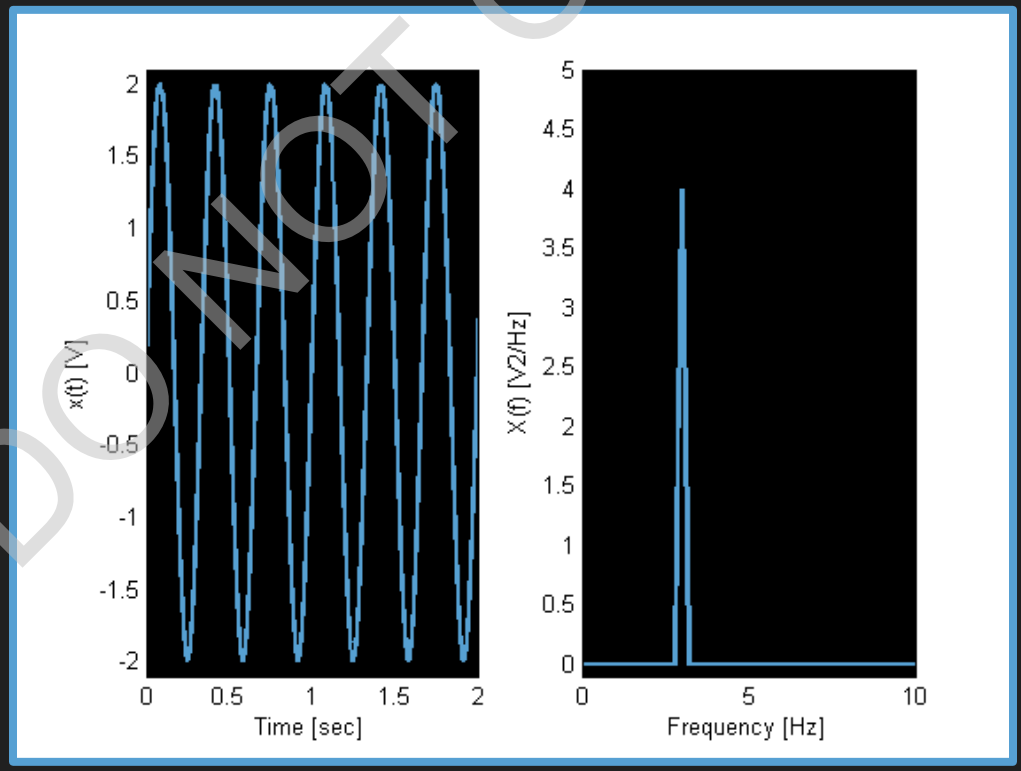
Caution: Most tACS literature refers to the peak-to-peak amplitude as amplitude.

NETWORK DYNAMICS

1. Raw trace.
2. Spectrum: Power as a function of frequency.
3. Spectrogram: Spectrum as a function of time.
4. Coherence: Interaction between two sites as a function of frequency.

Raw Trace

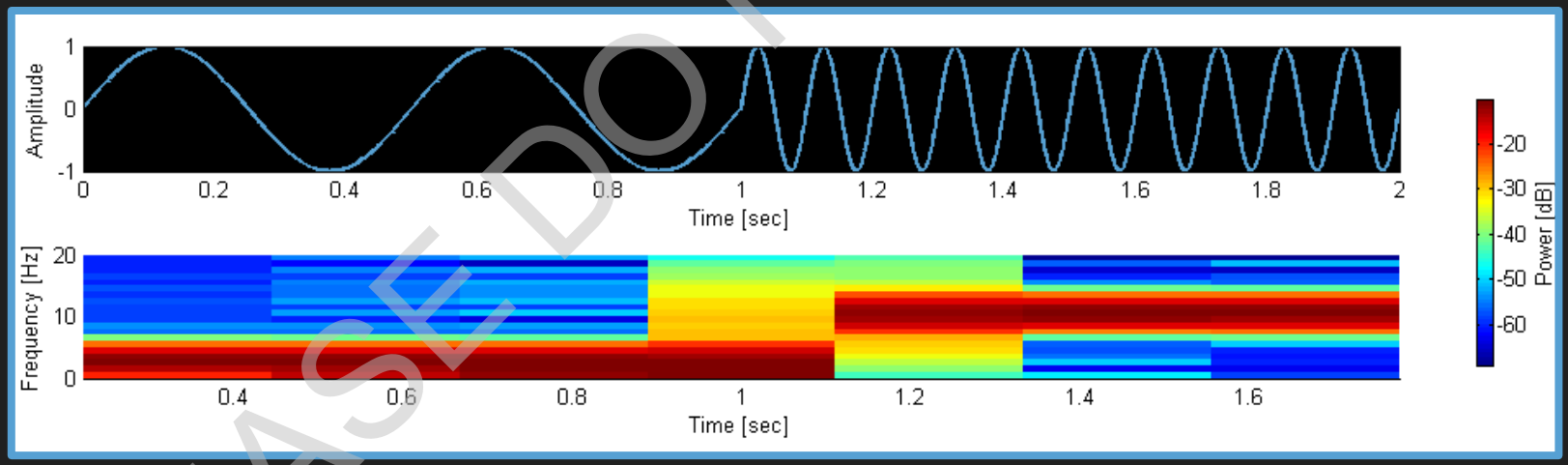
Spectrum



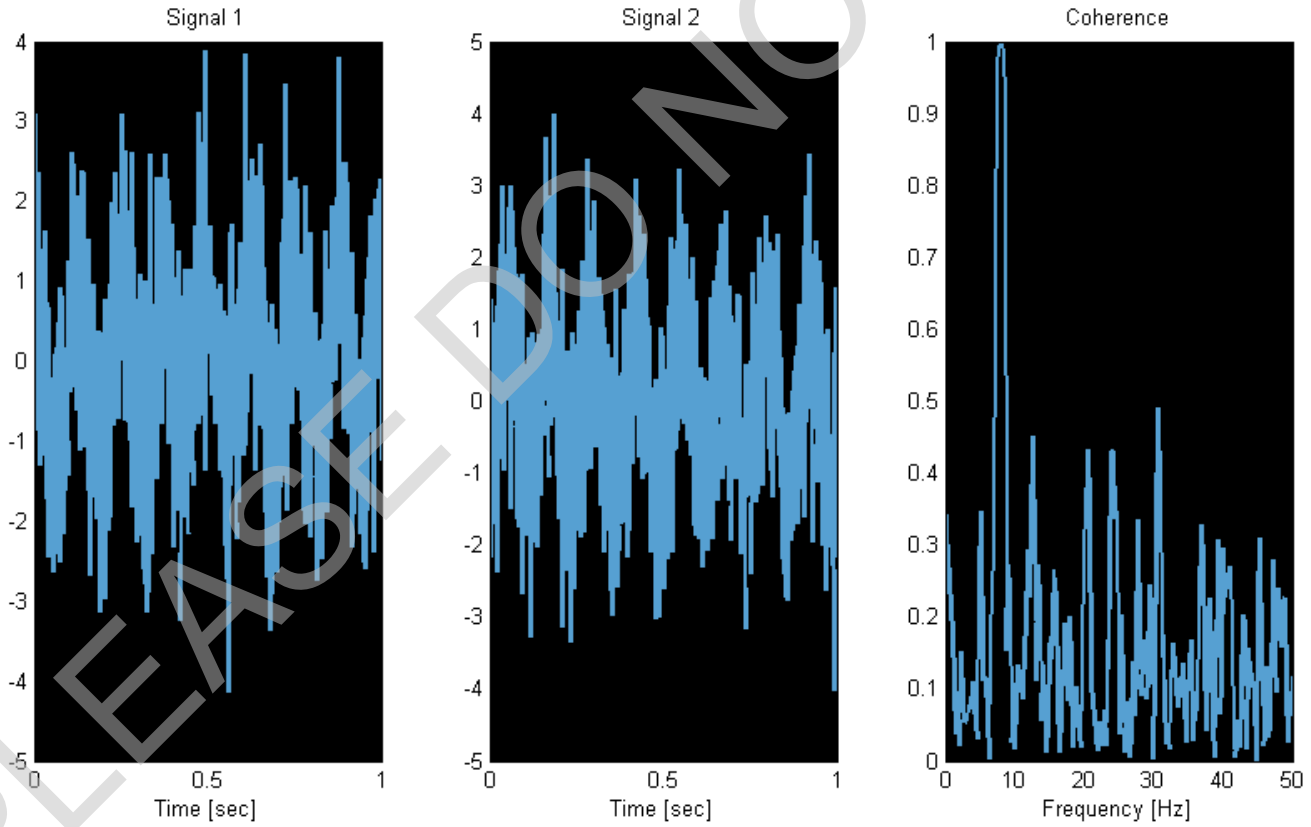
1. Raw trace.
2. Spectrum: Power as a function of frequency.
3. Spectrogram: Spectrum as a function of time.

Raw Trace

Spectrogram



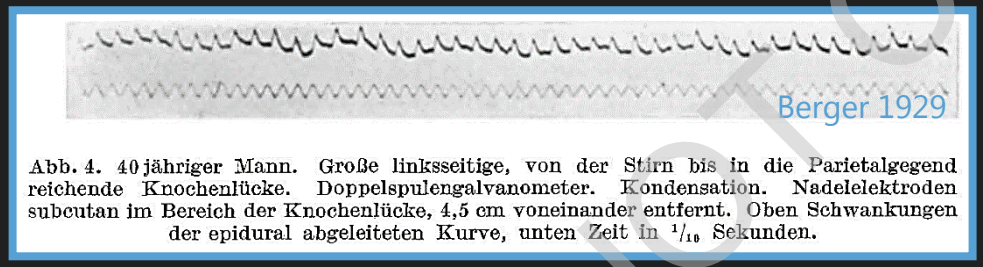
1. Raw trace.
2. Spectrum: Power as a function of frequency.
3. Spectrogram: Spectrum as a function of time.
4. Coherence: Interaction between two sites as a function of frequency.



Lesson #6

Brain rhythms effectively targeted by rhythmic brain stimulation
#MiddleSchoolMath

TARGETING BRAIN NETWORK DYNAMICS



Berger 1929

Abb. 4. 40jähriger Mann. Große linksseitige, von der Stirn bis in die Parietalgegend reichende Knochenlücke. Doppelspulengalvanometer. Kondensation. Nadelelektroden subcutan im Bereich der Knochenlücke, 4,5 cm voneinander entfernt. Oben Schwankungen der epidural abgeleiteten Kurve, unten Zeit in $^1/_{10}$ Sekunden.

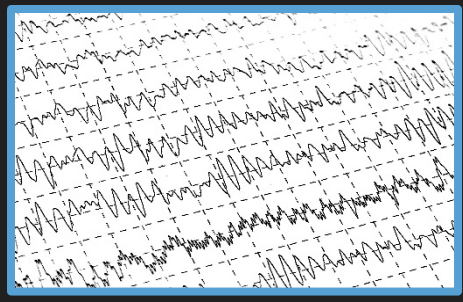
Neuroconn

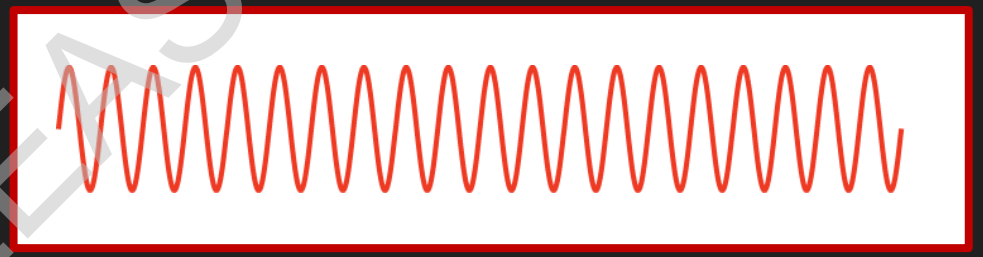
Write / Input

tACS

Read / Output

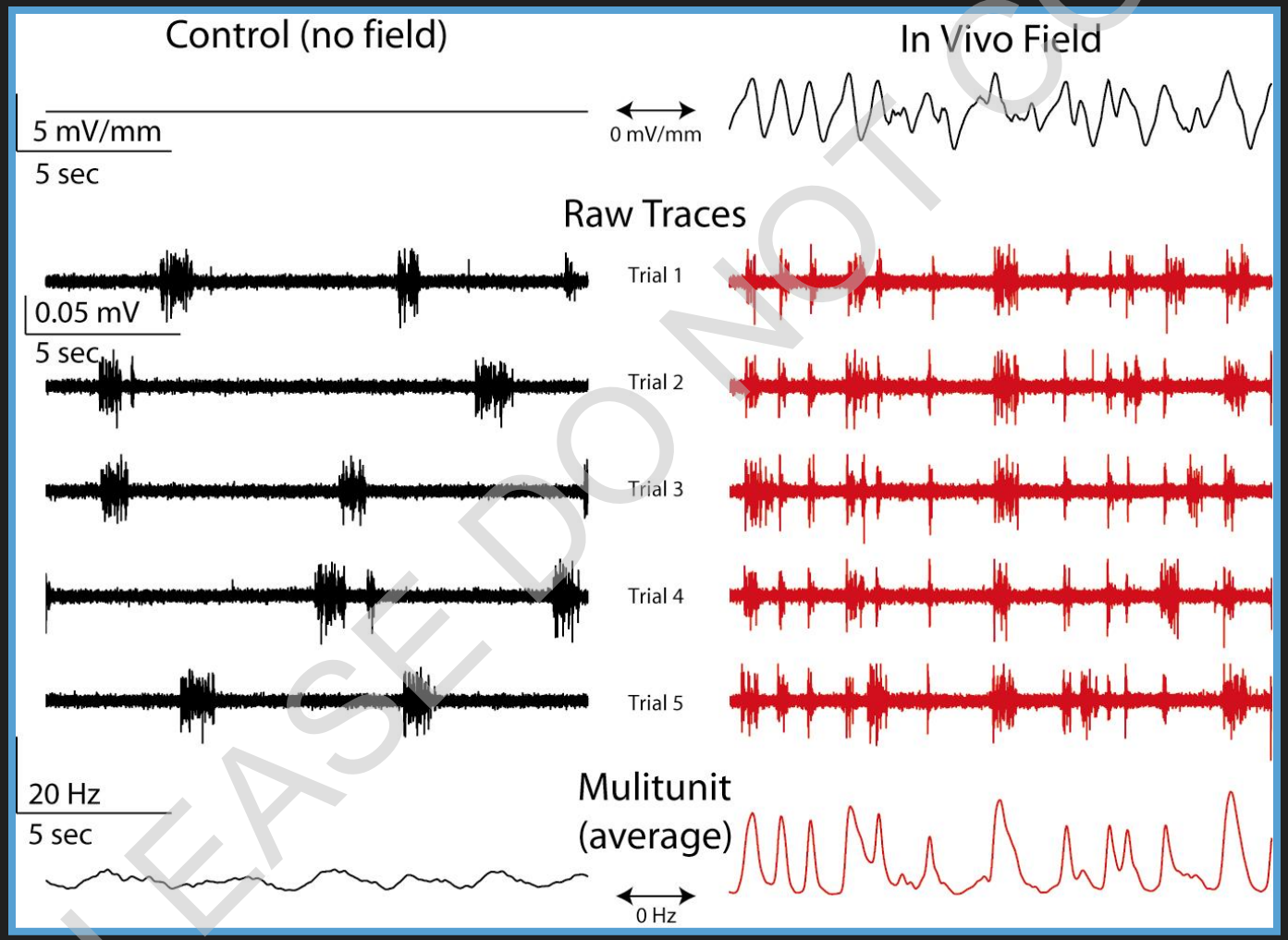
EEG





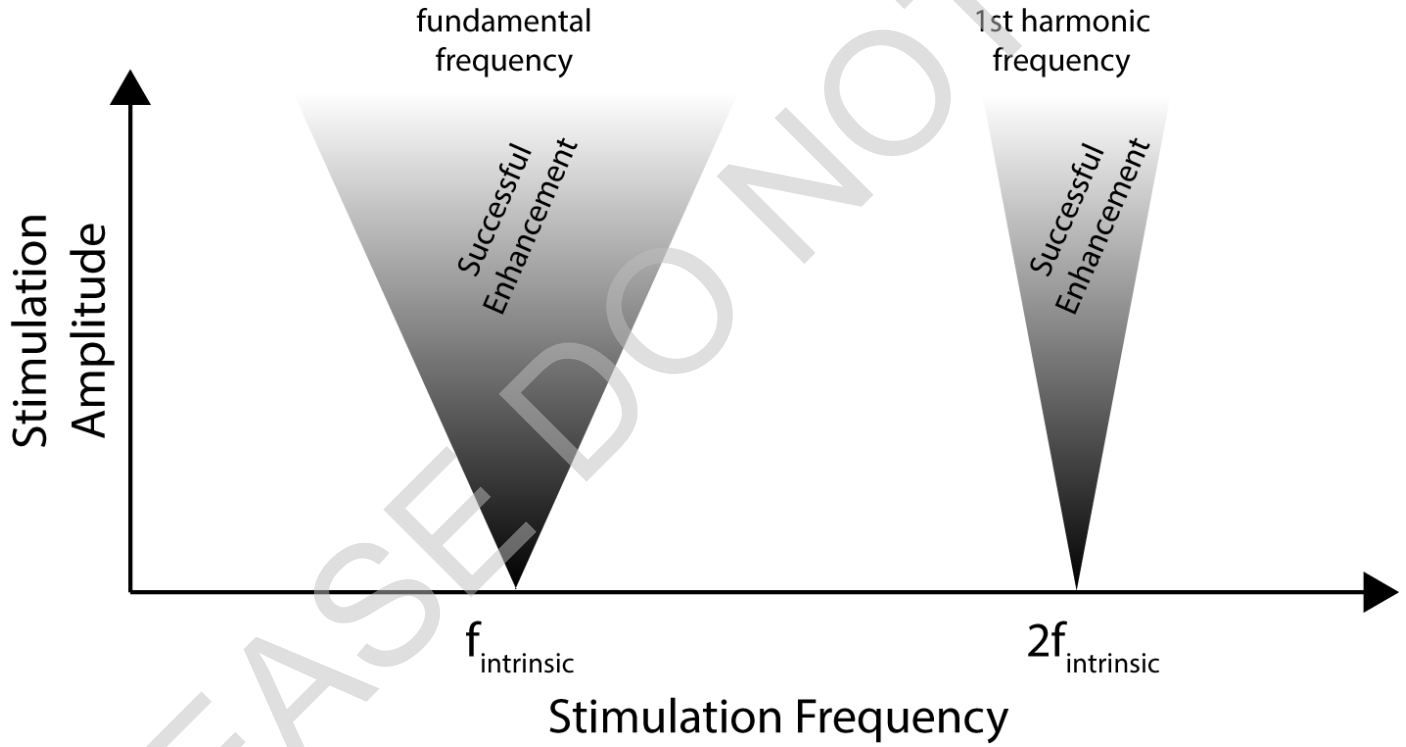
Transcranial Alternating Current Stimulation (tACS)

NATURALISTIC ELECTRIC FIELDS



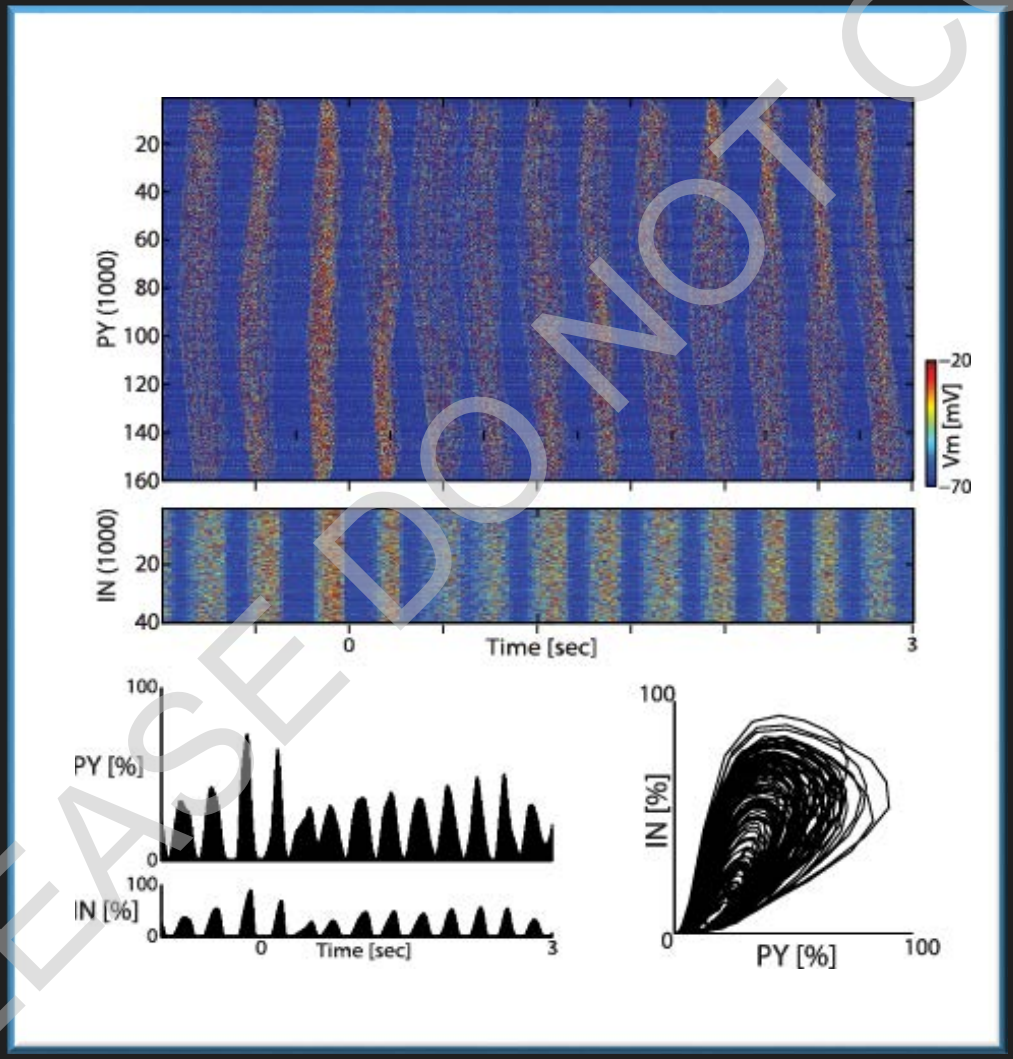
Frohlich and McCormick. 2010

ARNOLD TONGUE



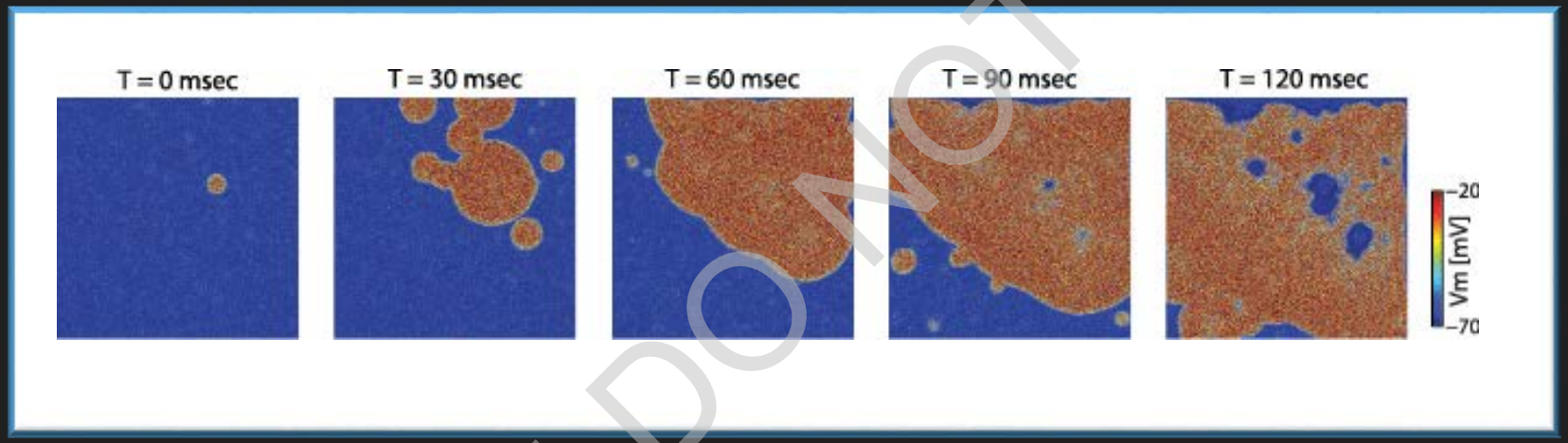
Frohlich 2014

SPIKING NEURAL MODEL (NETWORK)



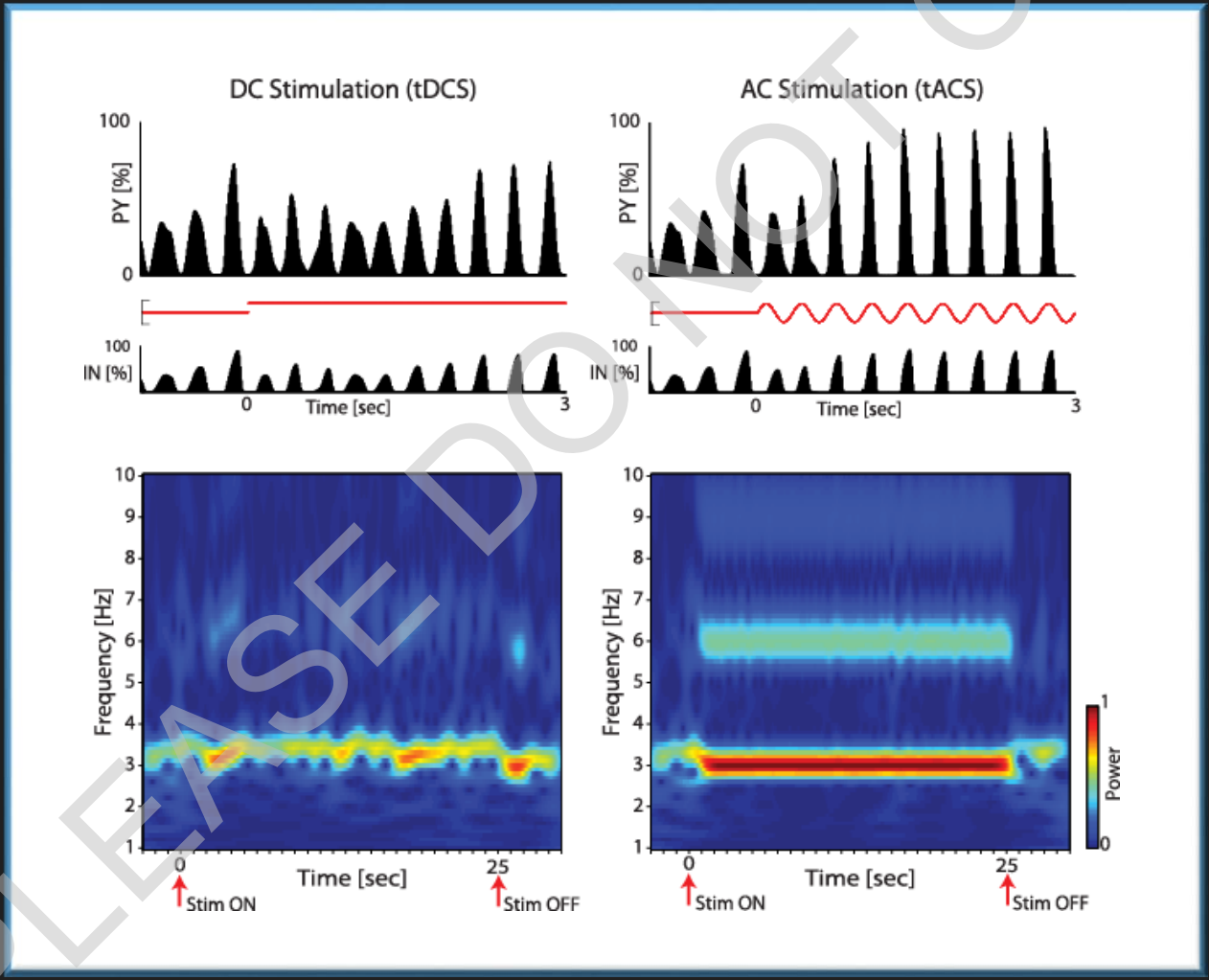
Ali et al. 2013

SPATIO-TEMPORAL DYNAMICS



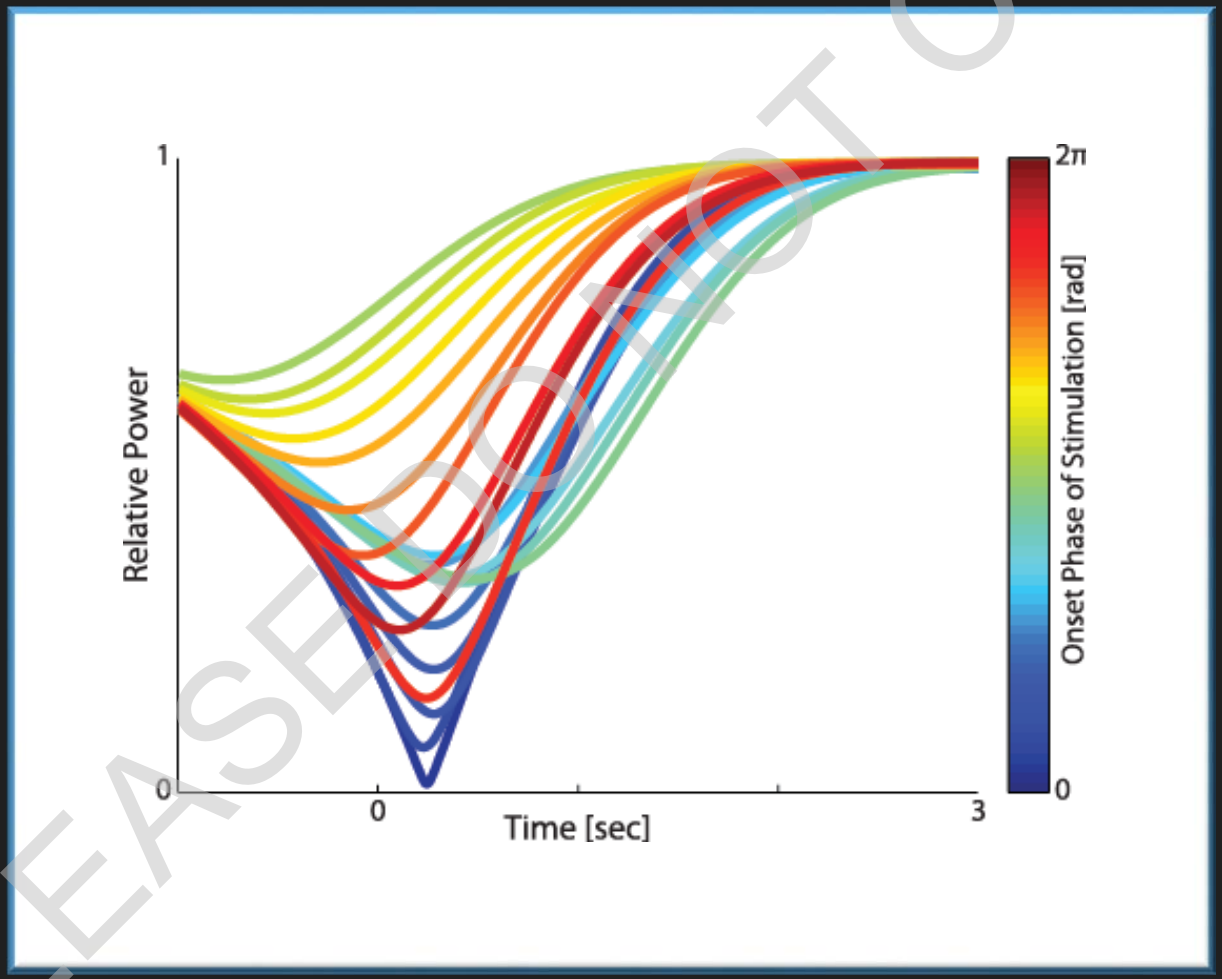
Ali et al. 2013

AC/DC



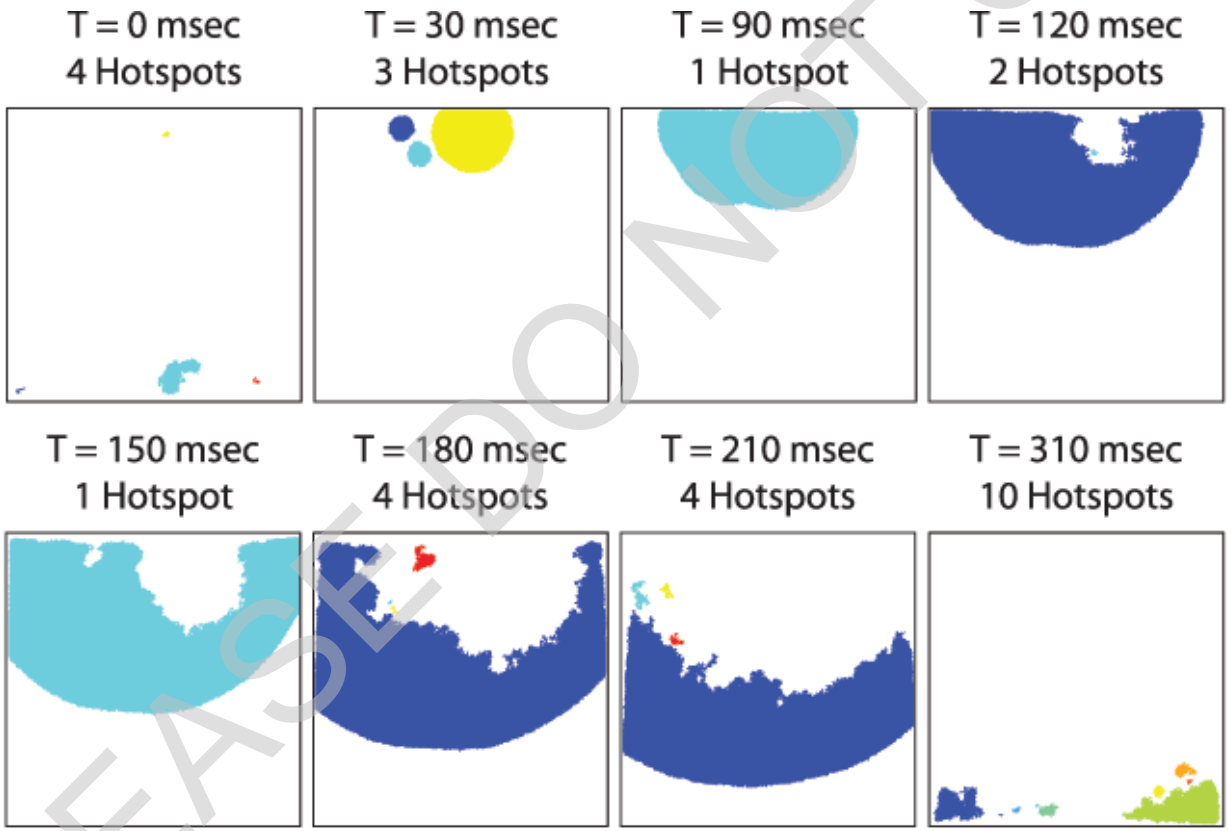
Ali et al. 2013

STIMULATION PHASE



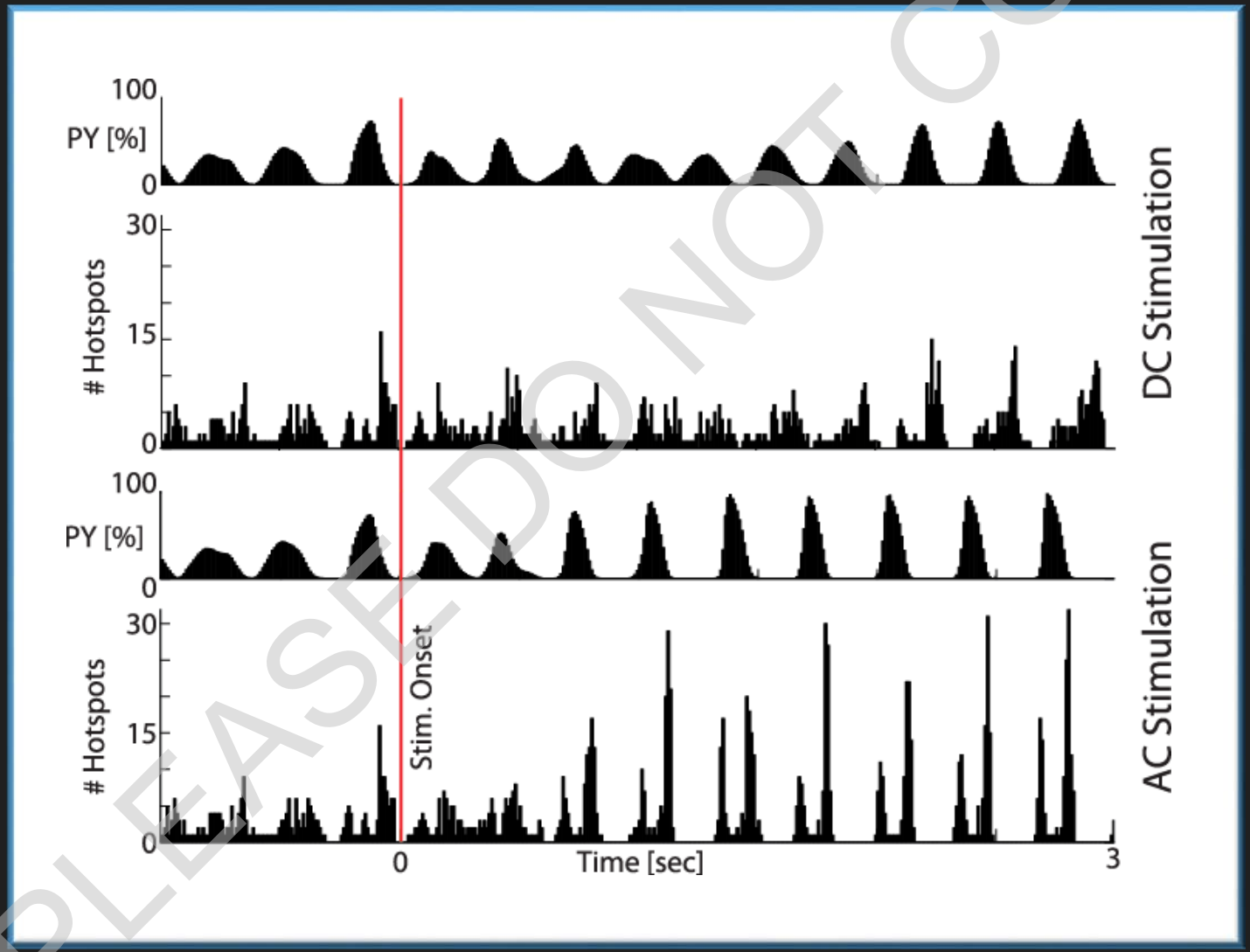
Ali et al. 2013

HOTSPOTS



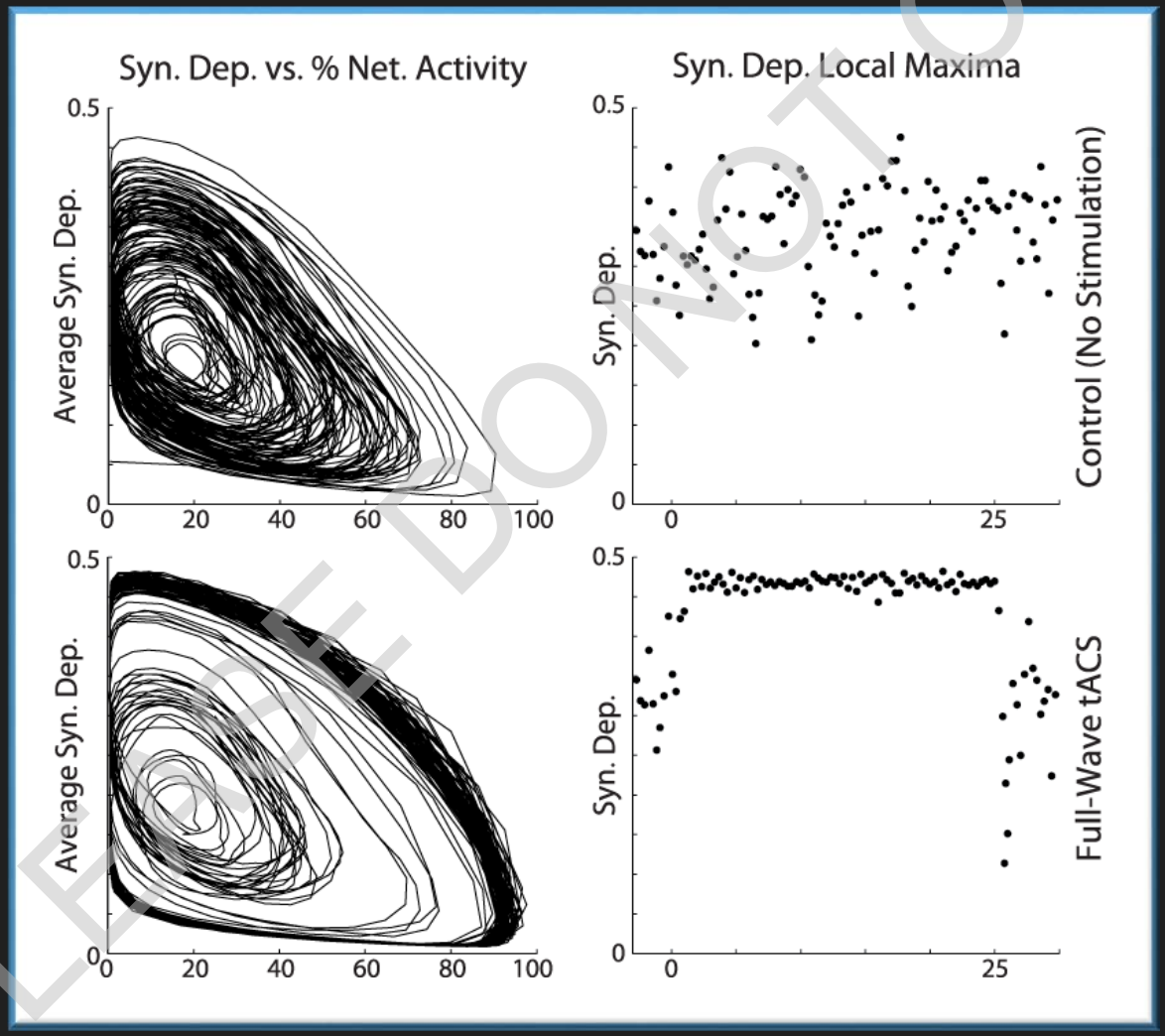
Ali et al. 2013

NETWORK-LEVEL MECHANISM



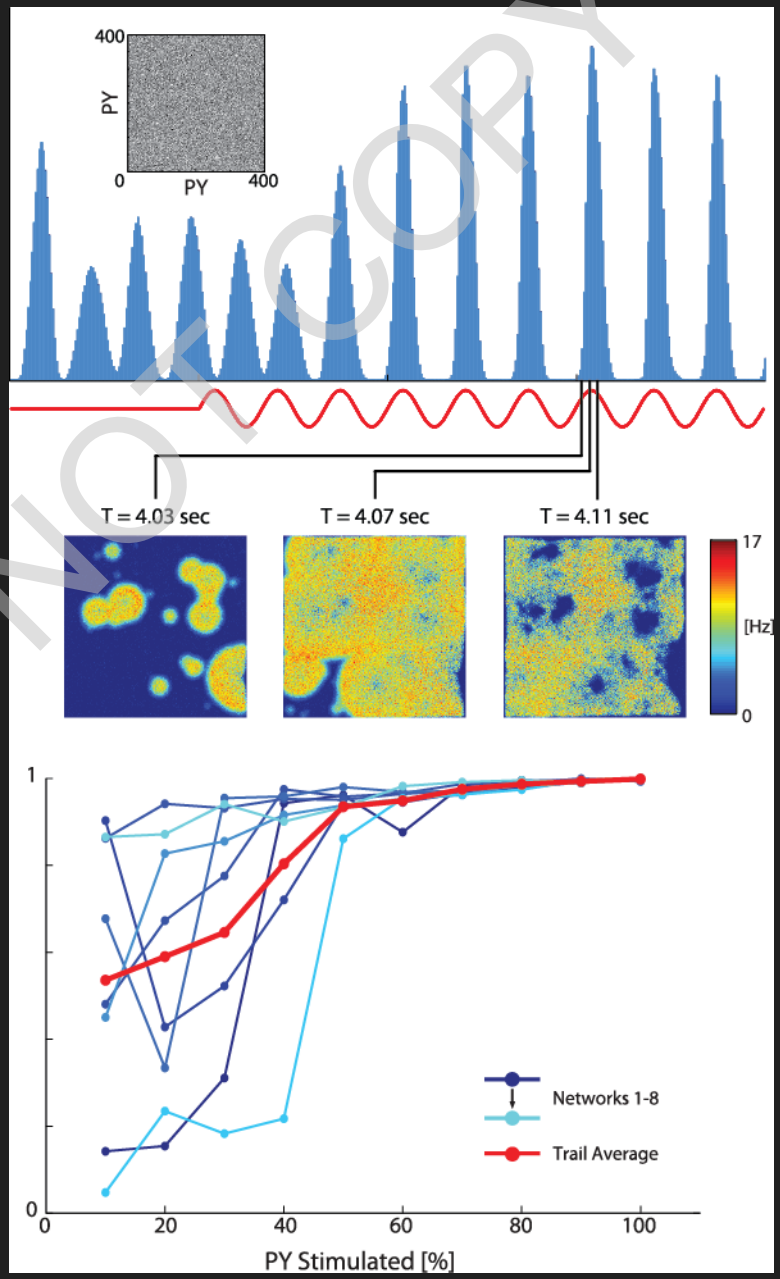
Ali et al. 2013

CELLULAR-LEVEL MECHANISM



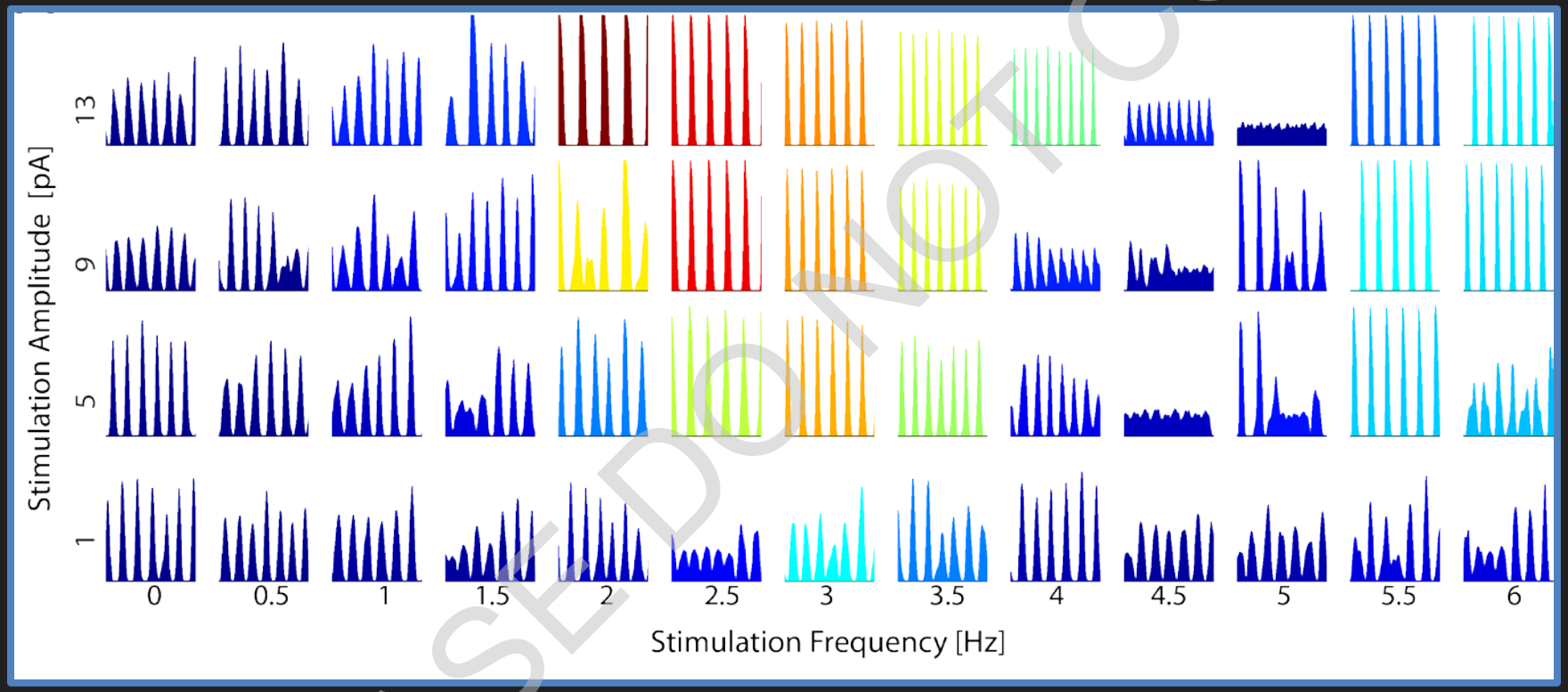
Ali et al. 2013

TARGETING A SUBPOPULATION



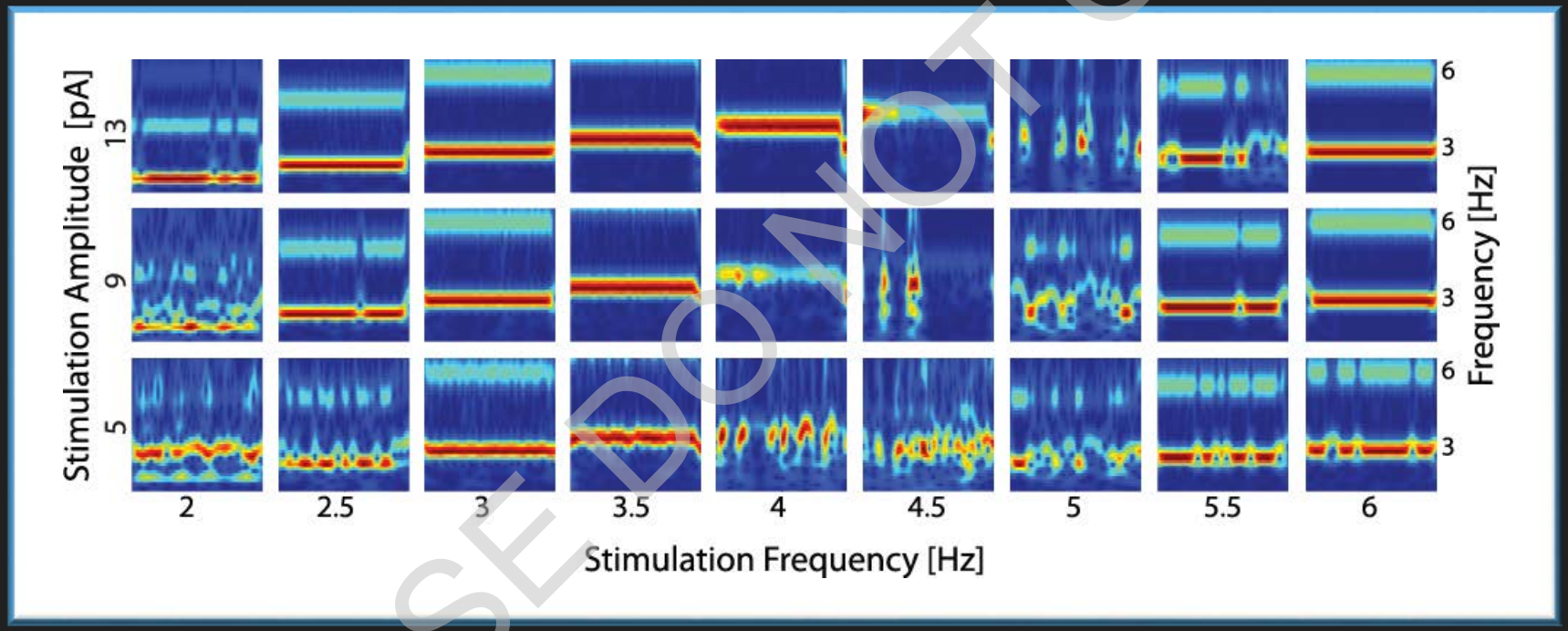
Ali et al. 2013

NETWORK RESONANCE

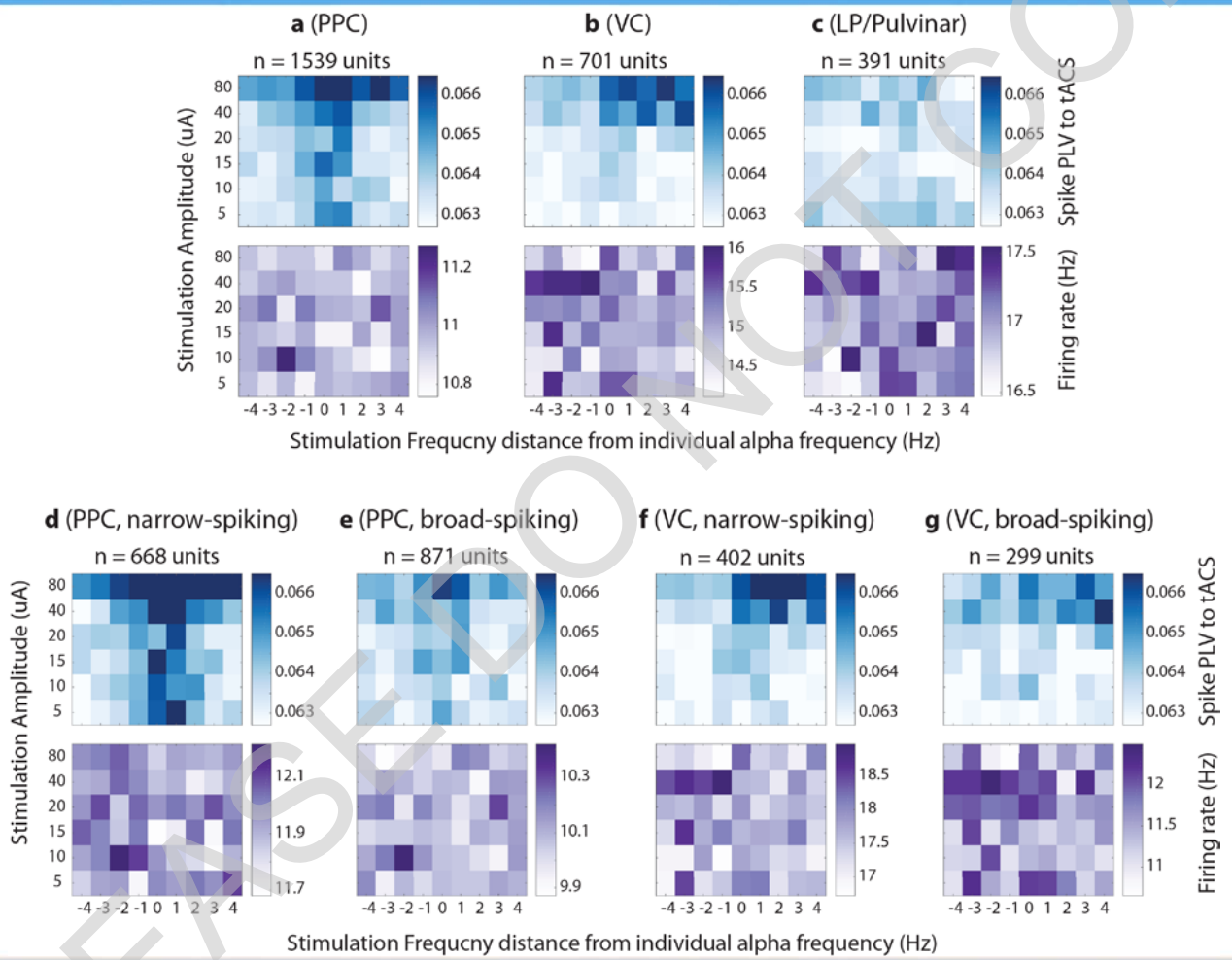


Ali et al. 2013

PHASE SLIPPING

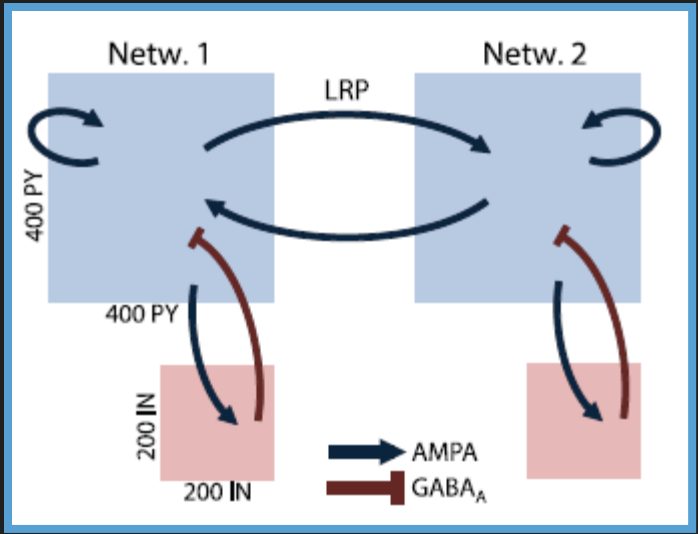


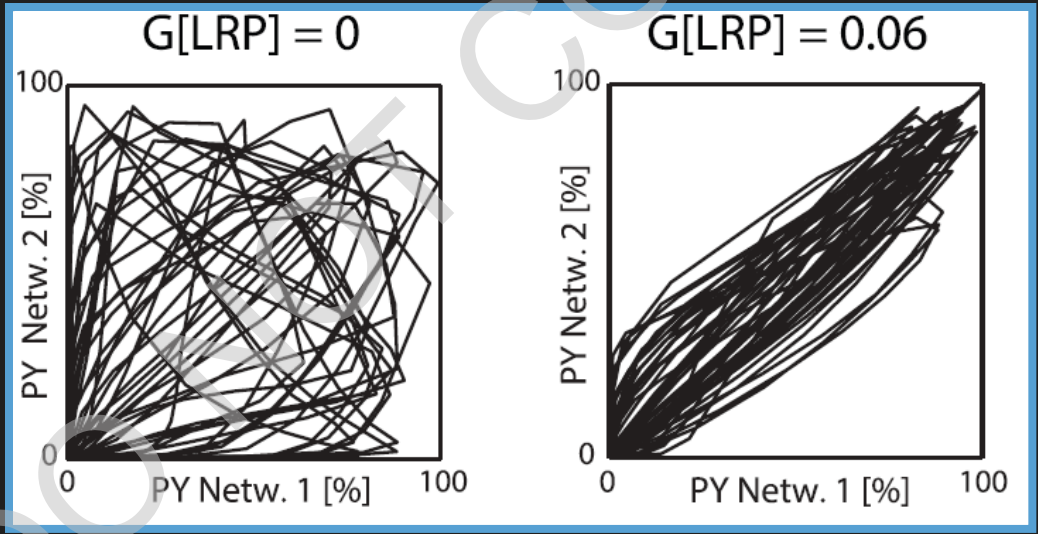
Ali et al. 2013

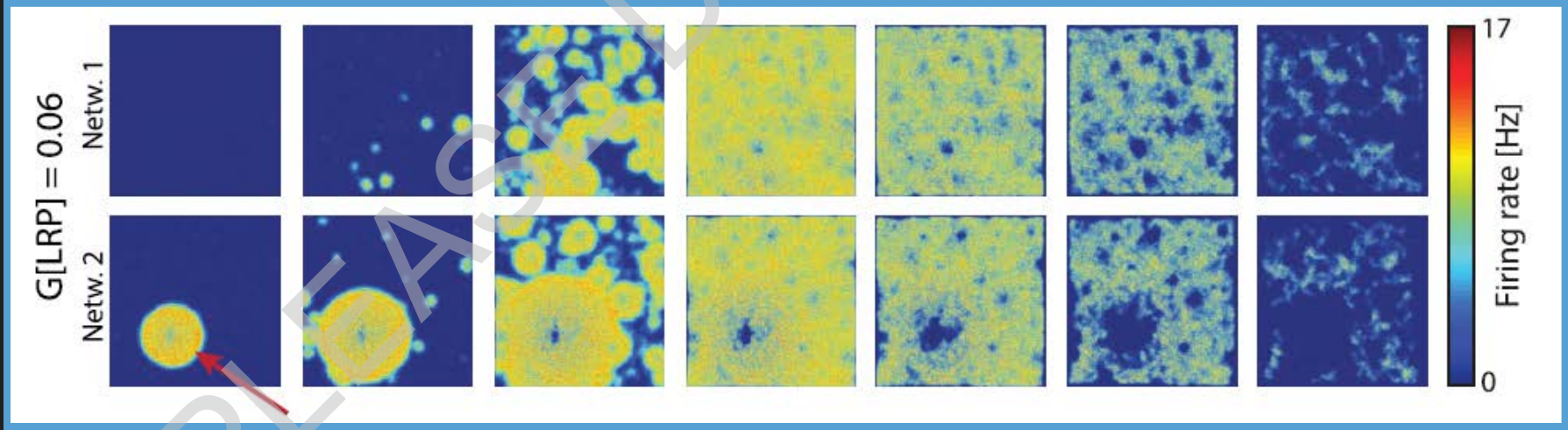


Negahbani et al. (2019, BioAxiv)

INTERACTING NETWORKS

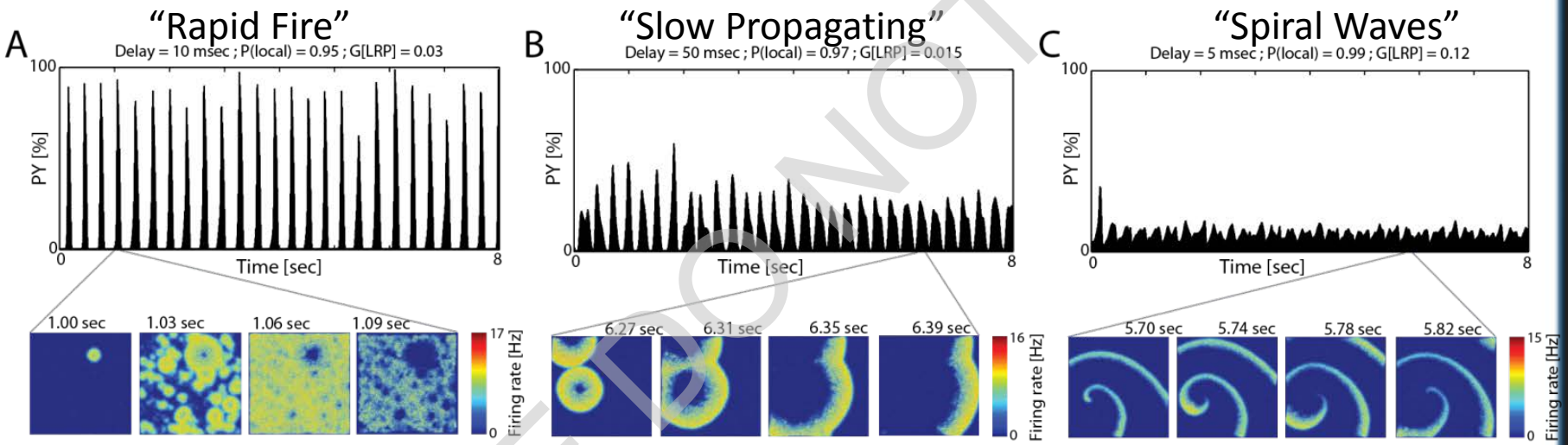






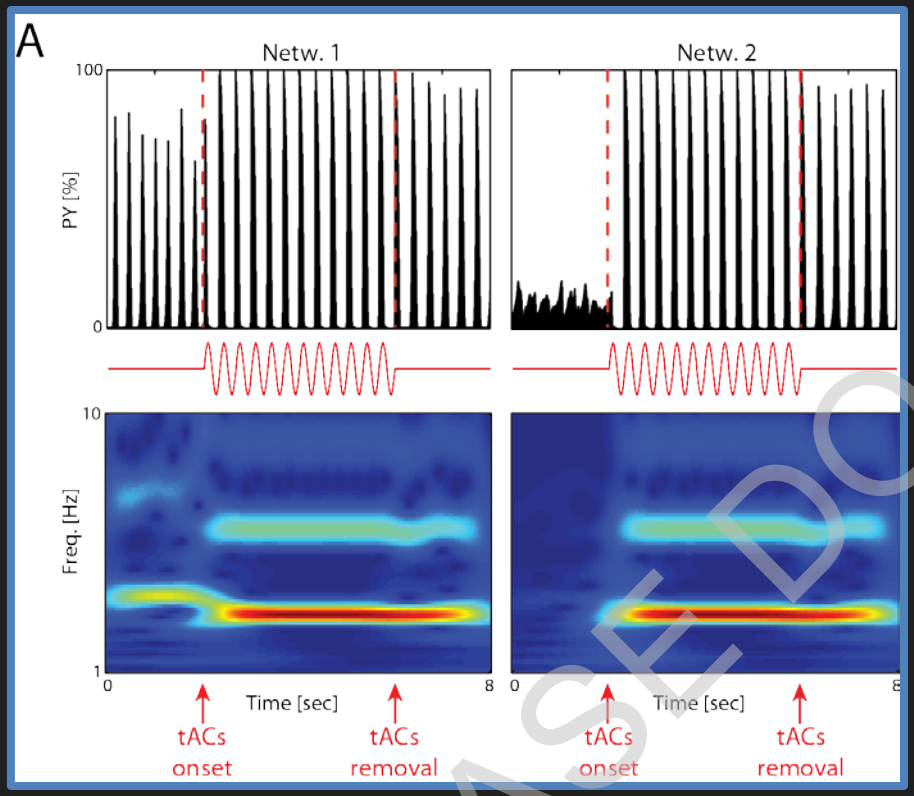
Kutchko and Frohlich 2013

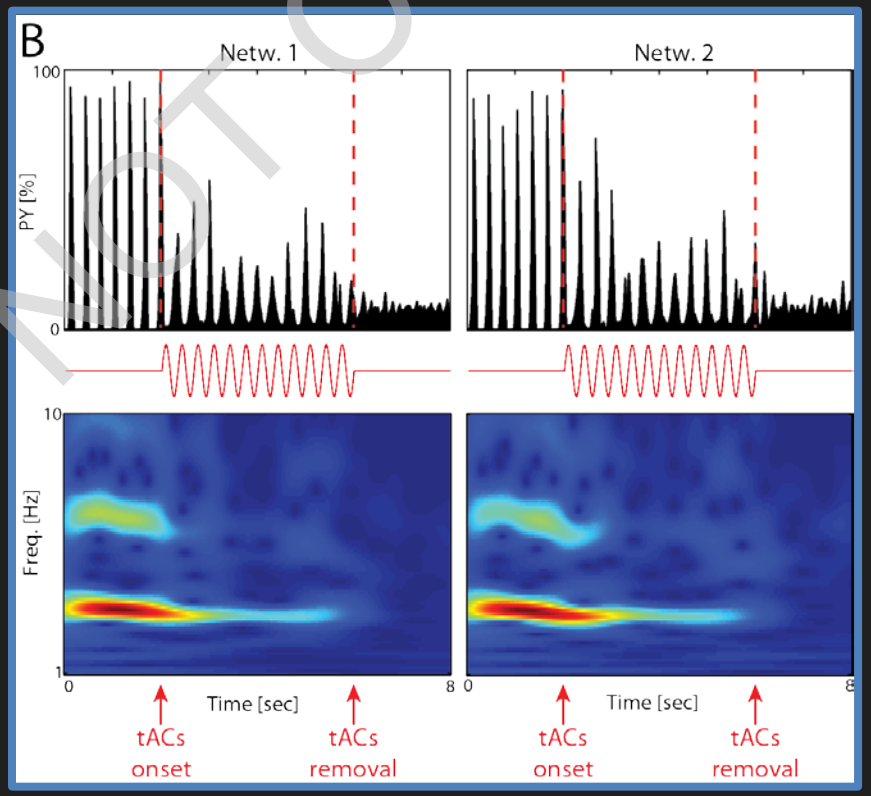
MULTISTABILITY



Kutchko and Frohlich 2013

STATE SWITCHING BY tACS





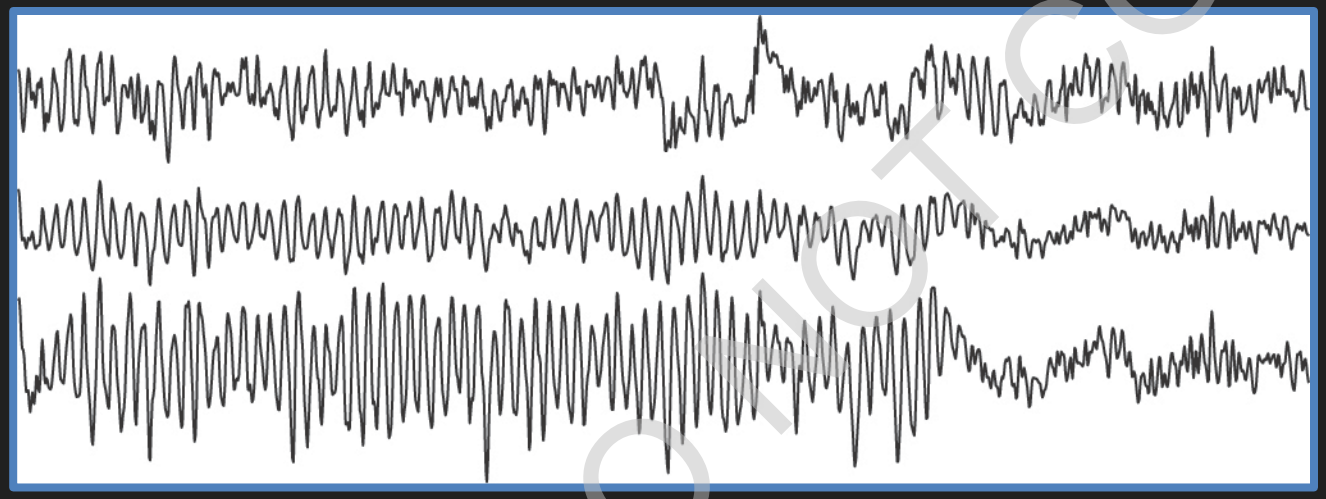
Kutchko and Frohlich 2013

Lesson #7

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

#MultiStability

TARGET: ALPHA OSCILLATIONS

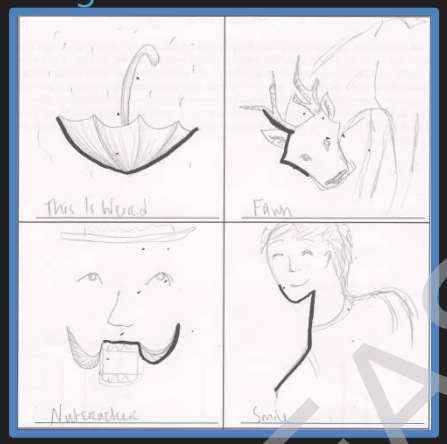


- "Offline" state, long-range functional connectivity, gating.
- Neurofeedback, rTMS (10 Hz), tACS, others…

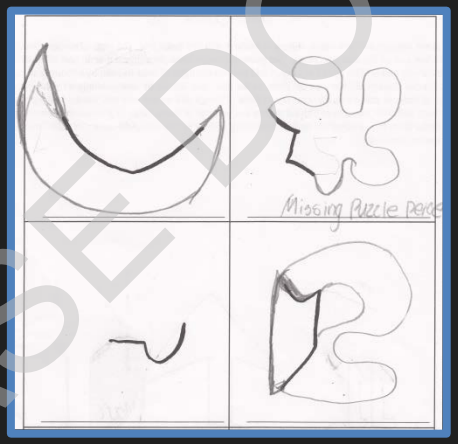
COGNITIVE ENHANCEMENT

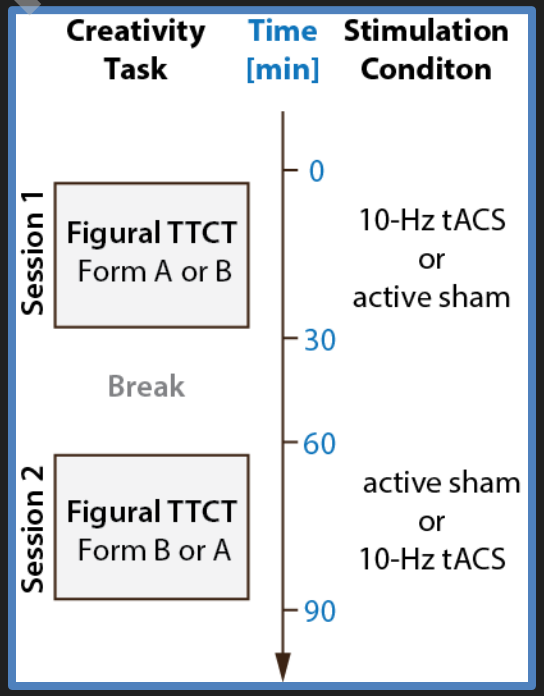
"increased alpha power during creative ideation is among the most consistent findings in neuroscientific research on creativity" (Fink and Benedek, 2010)

High Creative Ideation



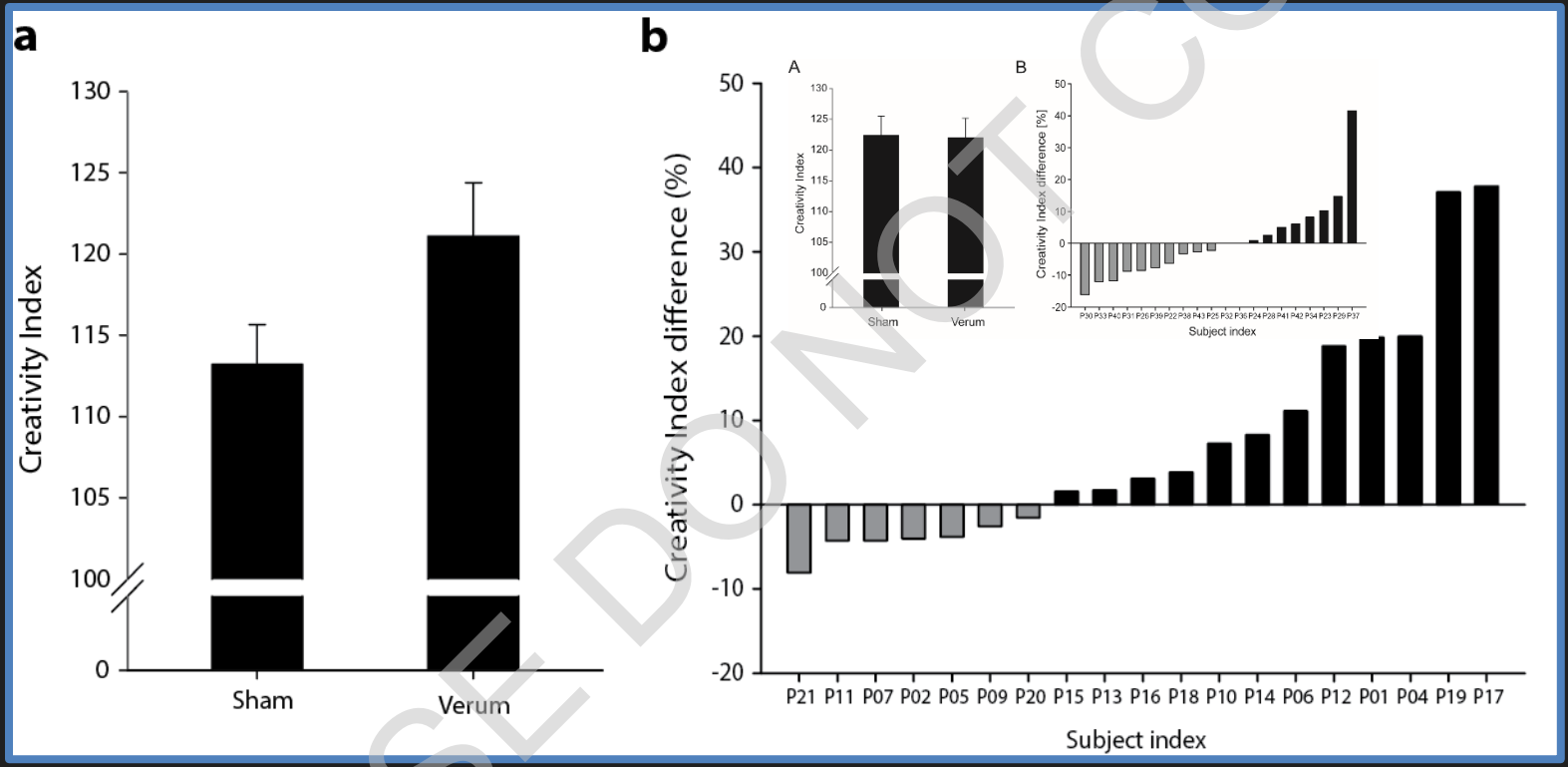
Low Creative Ideation





Lustenberger et al. (2015)

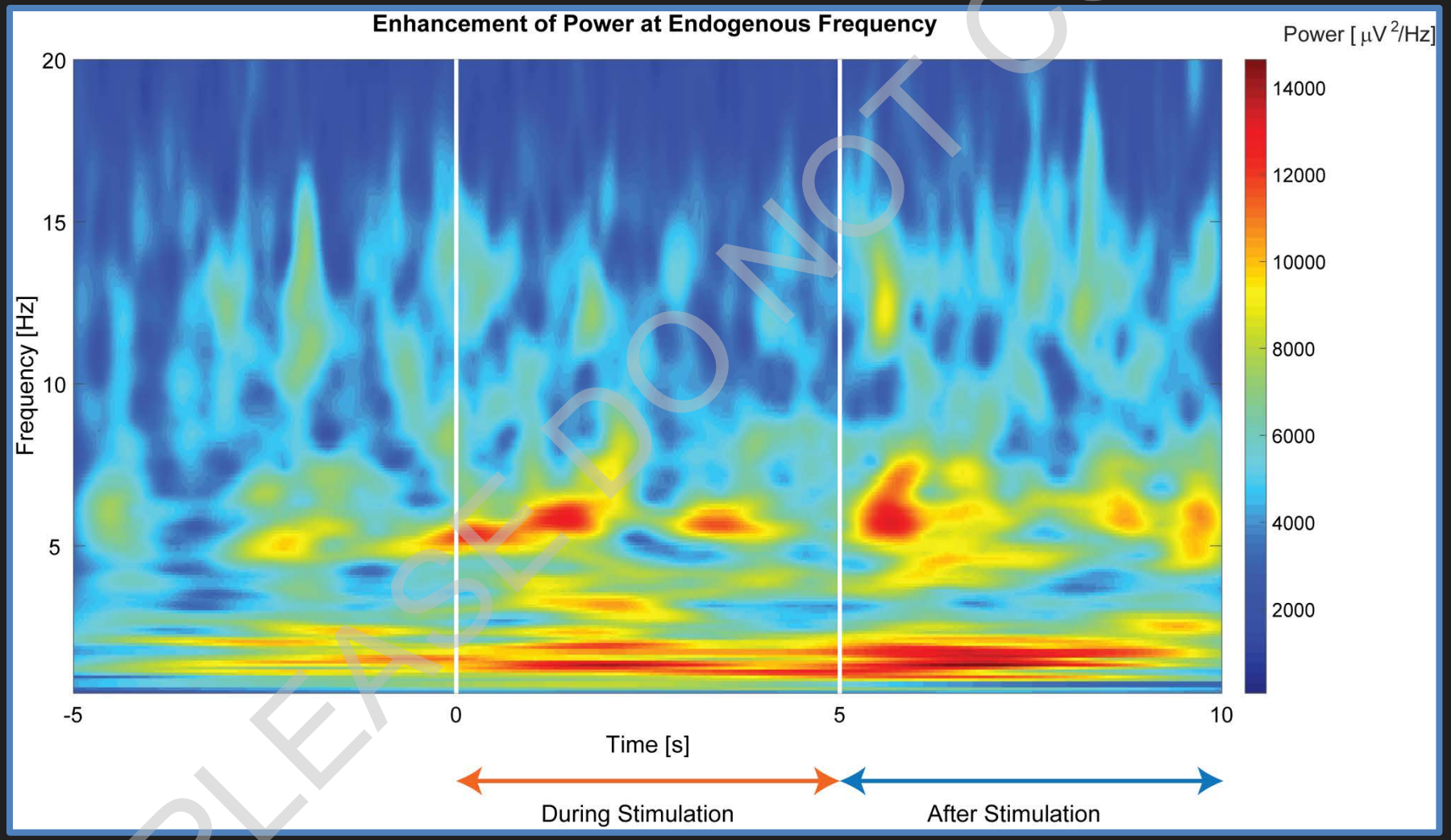
ENHANCING CREATIVITY



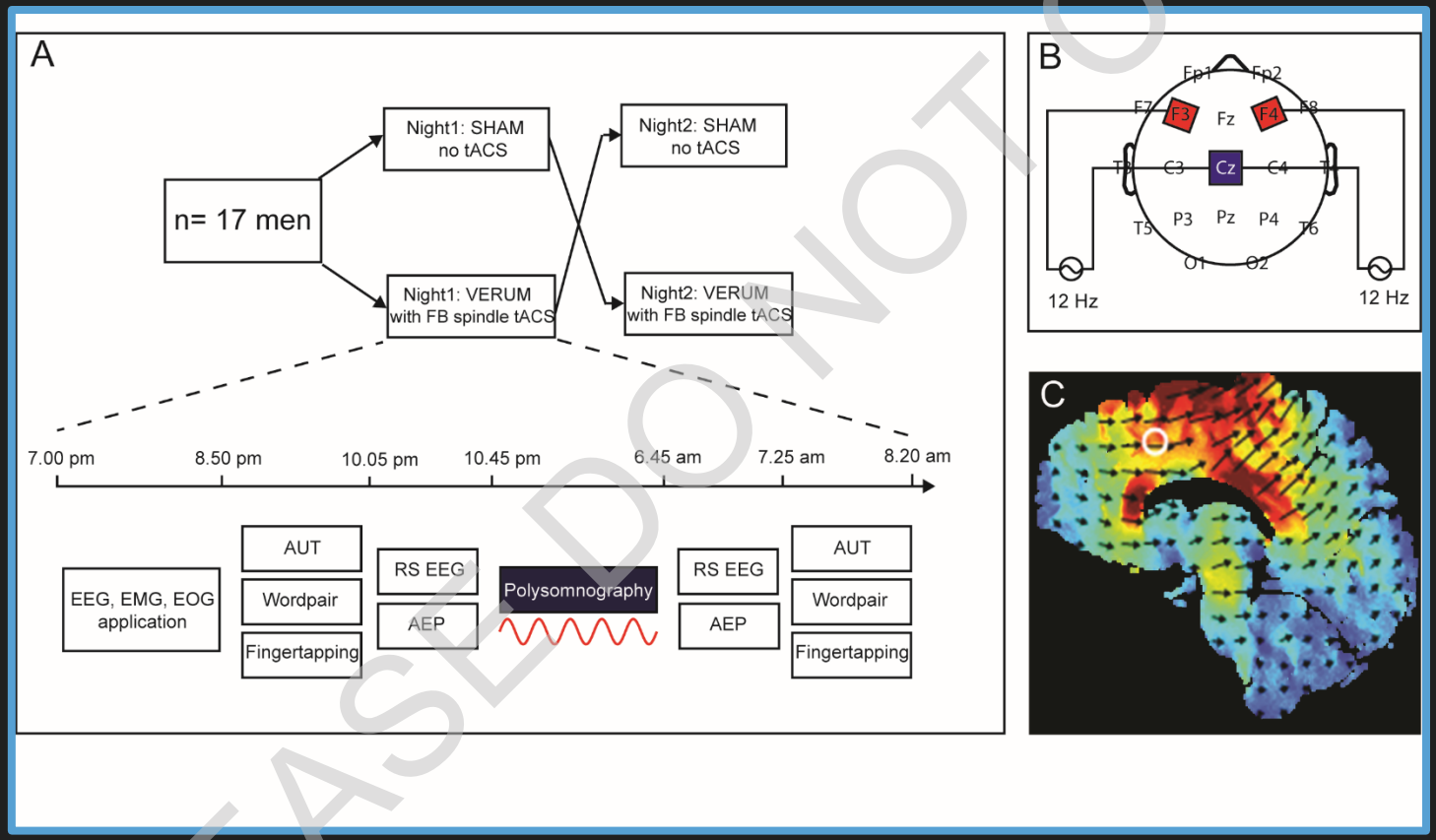
- Blinding was successful ($p > 0.2$).
- 10 Hz tACS significantly enhances creativity as measured by the Torrance Test of Creative Thinking (7.45 % ± 3.11 % S.E.M.; $F_{1,16} = 5.14$, $p = 0.036$).
- No enhancement with 40Hz-tACS.

Lustenberger et al. (2015)

OSCILLATION ENHANCEMENT

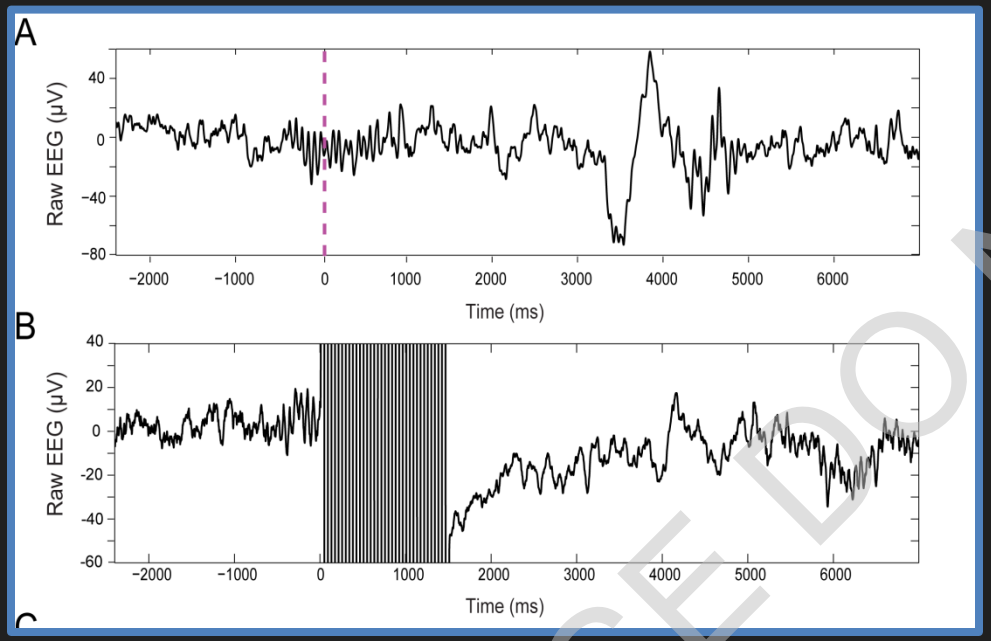


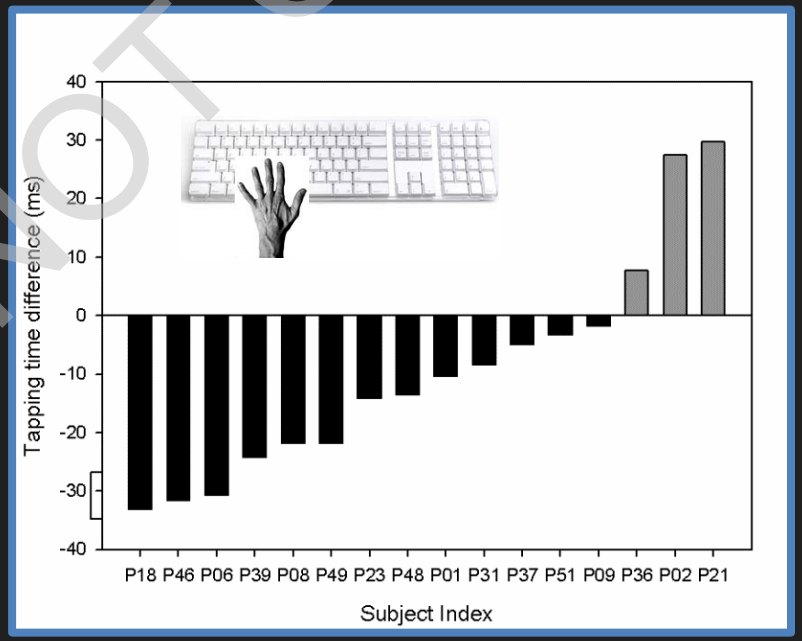
FEEDBACK tACS TO MODULATE SLEEP SPINDLES



Lustenberger et al. (2015)

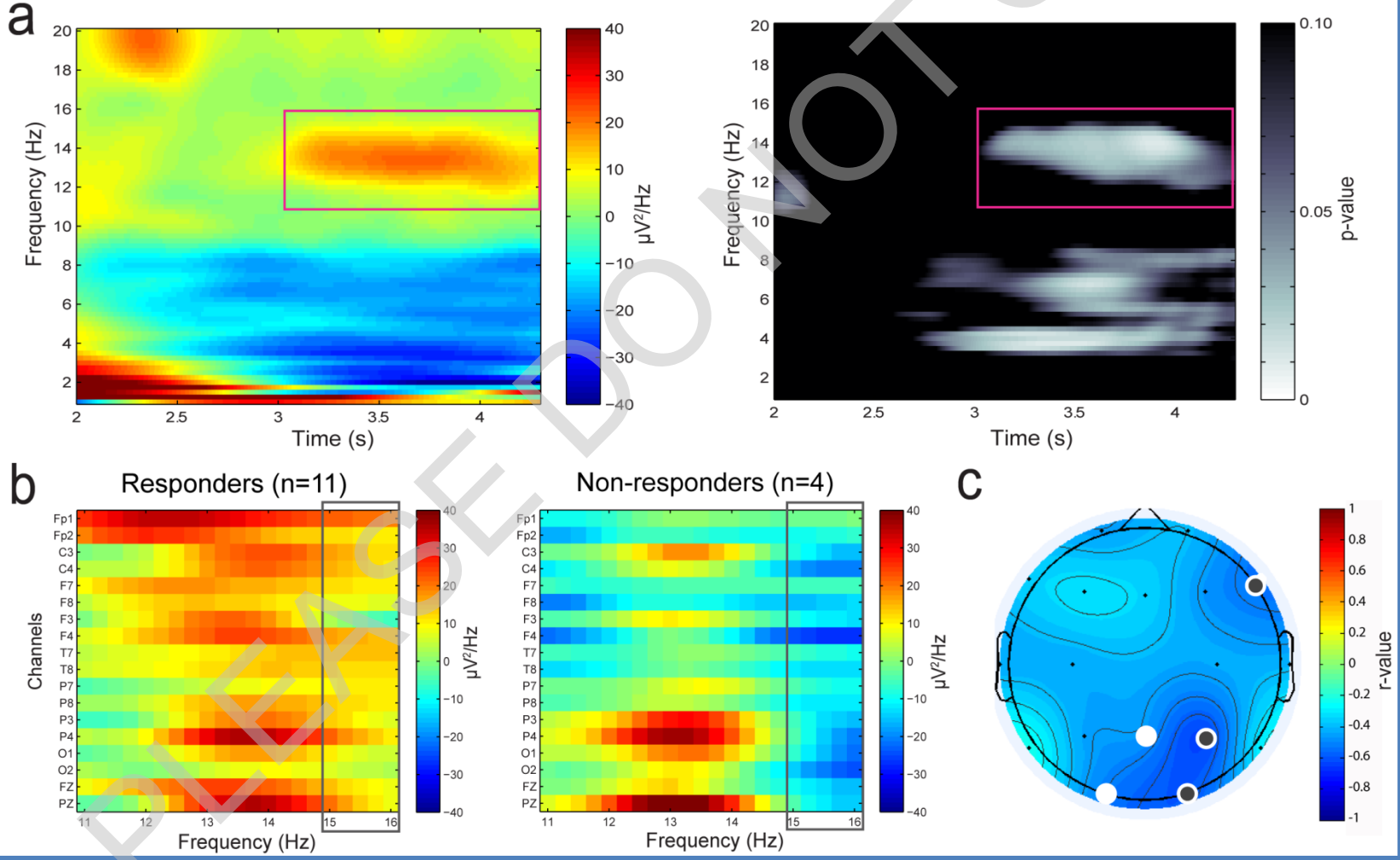
IMPROVING MEMORY CONSOLIDATION





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.

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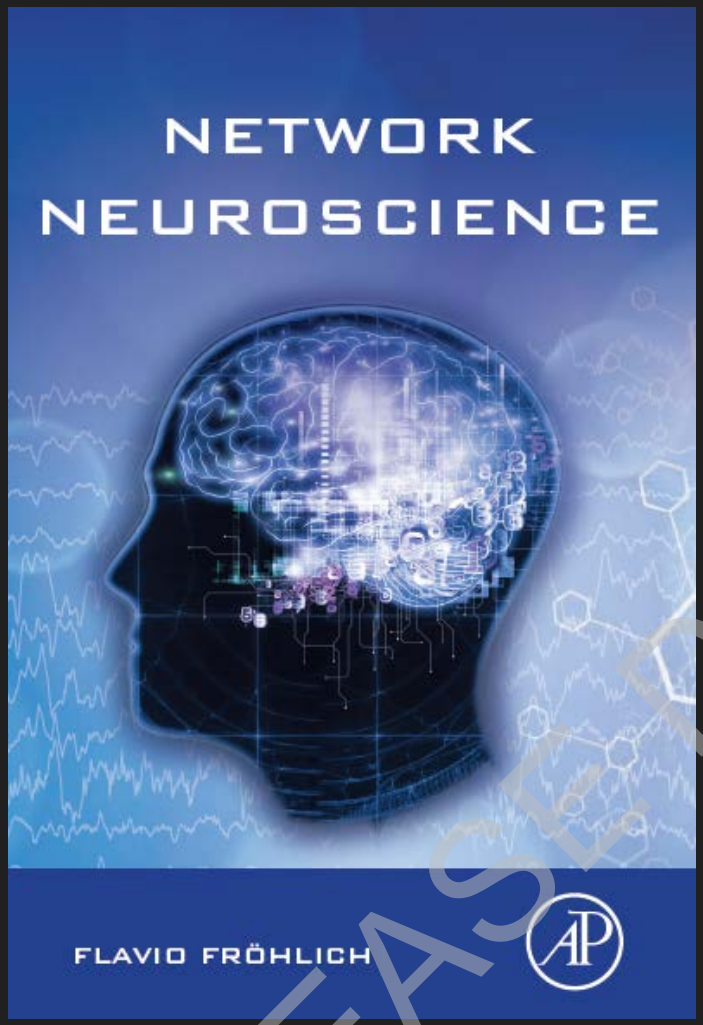

Neurons, Synapses, and Circuits.

Measuring, Perturbing, and Analyzing Brain Networks

Cortical Oscillations

Network Disorders

Toolboxes

Thank you for your attention.

flavio_frohlich@med.unc.edu
www.networkneuroscientist.org
@FrohlichLab