

Therapeutic Uses of Noninvasive Brain Stimulation *Current & Developing*

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Harvard Catalyst

Beth Israel Deaconess Medical Center • Harvard Medical School



Beth Israel Deaconess
Medical Center

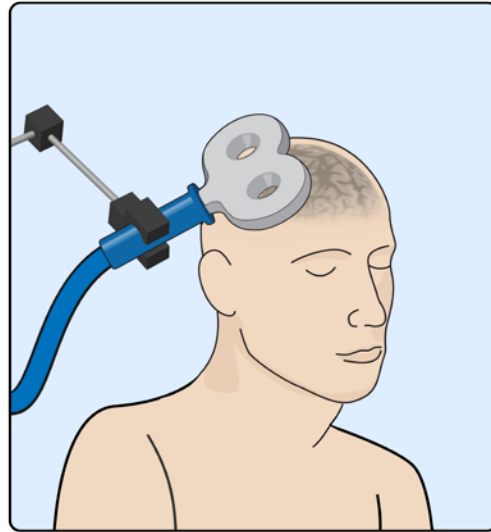


Disclosure

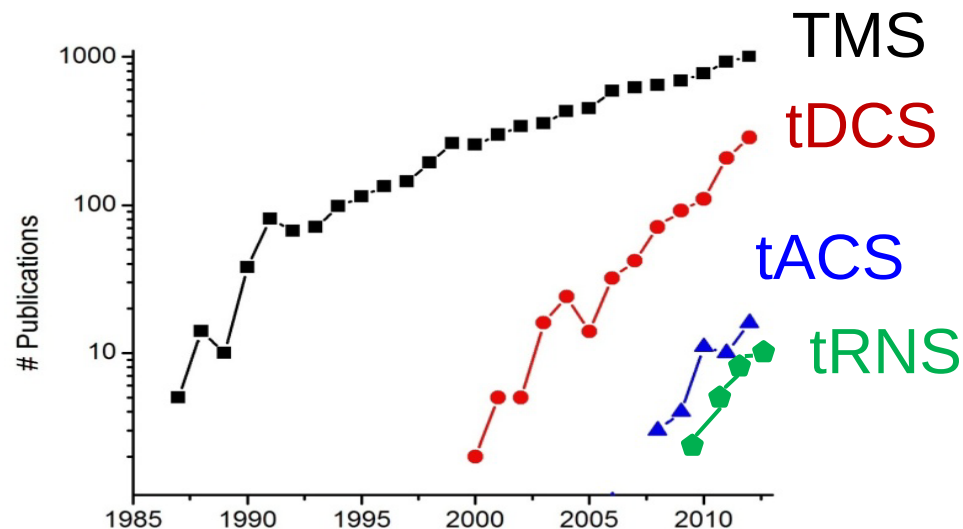
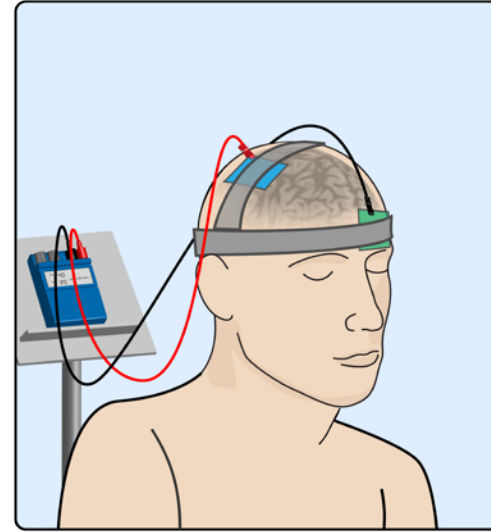
- Scientific Advisory Board Member for Neuronix, Nexstim, Neosync, Magstim, Neuroelectronics, Starlab, Axilium Robotics
- Serve on Device Expert Panel at FDA
- Funding from National Institutes of Health, National Science Foundation, Michael J Fox Foundation, Sidney-Baer Foundation
- I will talk about off-label applications
- Listed inventor on various patents on combination of TMS with EEG and fMRI

Noninvasive Brain Stimulation

Transcranial
Magnetic
Stimulation
(TMS)



Transcranial
Current
Stimulation
(tCS)
tDCS, tACS, tRNS



FDA approved Treatment for Medication-Resistant Depression



Brainstorm



Medicare & Insurance Covered

TMS for Medication-Resistant Depression

Changing Lives !

- >600 systems in clinical use in the US
- 250 days/year & 5 patients/day
- = *750,000 treatments per year*

- avg. 25 treatment sessions/patient
- = *30,000 patients per year*

- 30% remission rate
- = *9,000 remitters per year*
- *25 remitters per day*

Why do 40% of MDD Patients not respond to TMS ?



Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation

Beatrix Krause* and Roi Cohen Kadosh

Department of Experimental Psychology, University of Oxford, Oxford, UK

- Patient characteristics
 - *Genetic factors*
 - *Head-tissue morphology*
 - *'State' (fatigue, attention, alertness, ...)*
- Disease characteristics
 - *Symptom complex*
 - *Co-morbidities*
- Stimulation characteristics

tDCS for Medication-Resistant Depression

Study	N	Conditions	Conclusions
Palm et al Brain Stim 2012	22	Cross-over Left DLPFC vs sham 1-2 mA, 2 wks	Real = sham
Loo et al Biol Psych 2012	64	Left DLPFC anode vs sham 2 mA, 15 sessions over 3 wks	- Mood improved real>sham 13% responders in both groups - Cognitive improvements real>sham
Brunoni et al JAMA Psych 2013	120	Left DLPFC anode / R cathode (real or sham) + sertraline (50 mg/d) or placebo 2 mA, 6 wks	- tDCS+sertraline superior - Efficacy and safety of tDCS = sertraline
Martin et al J Affect Dis 2013	26	6 Month continuation Rx Left DLPFC anode Weekly x 3 months then monthly 2 mA, 6 wks	- Prevent relapse? 84% at 3 mo 51% at 6 mo

FDA approved for Abortive Treatment of Migraine

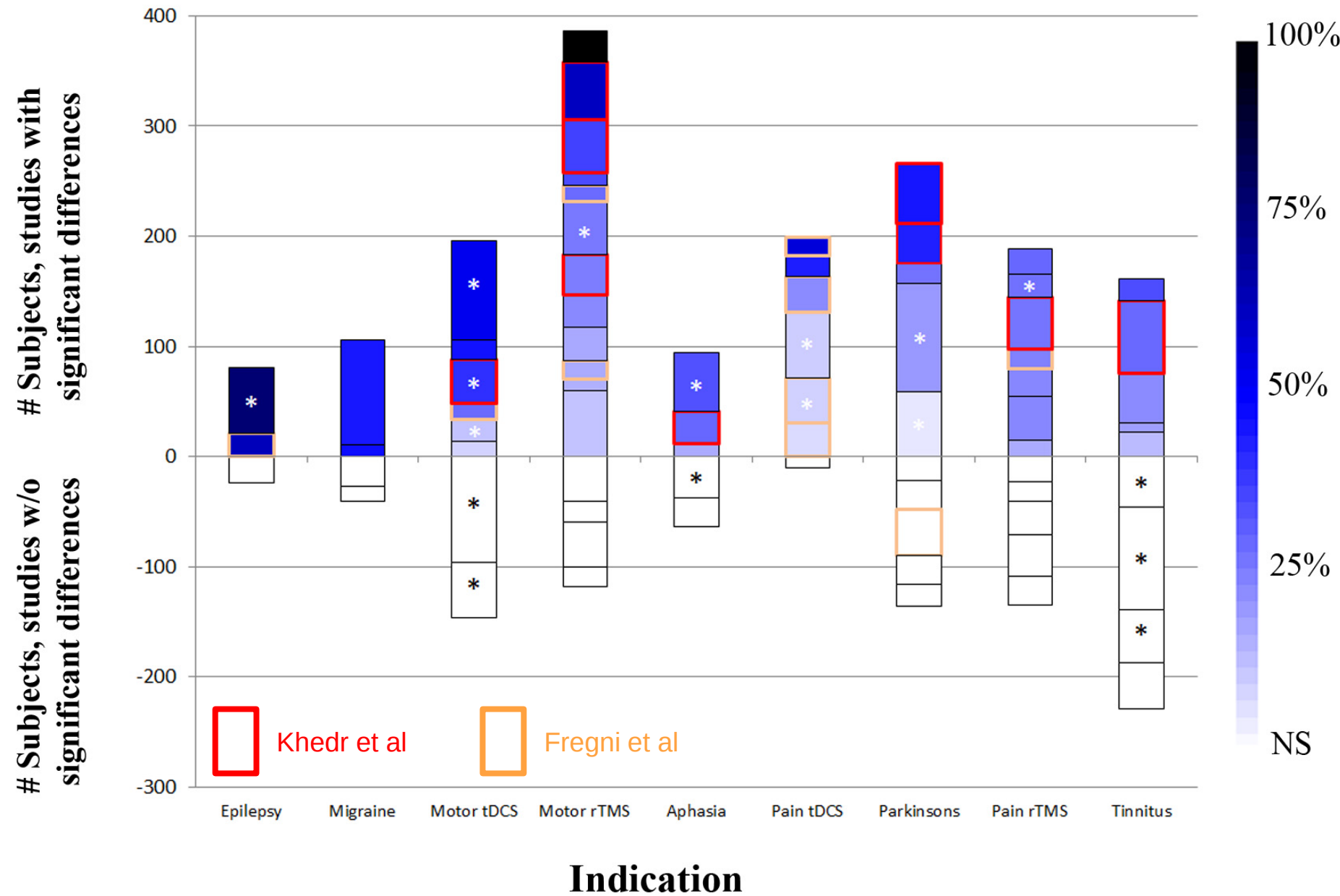


Paving the path
for home use

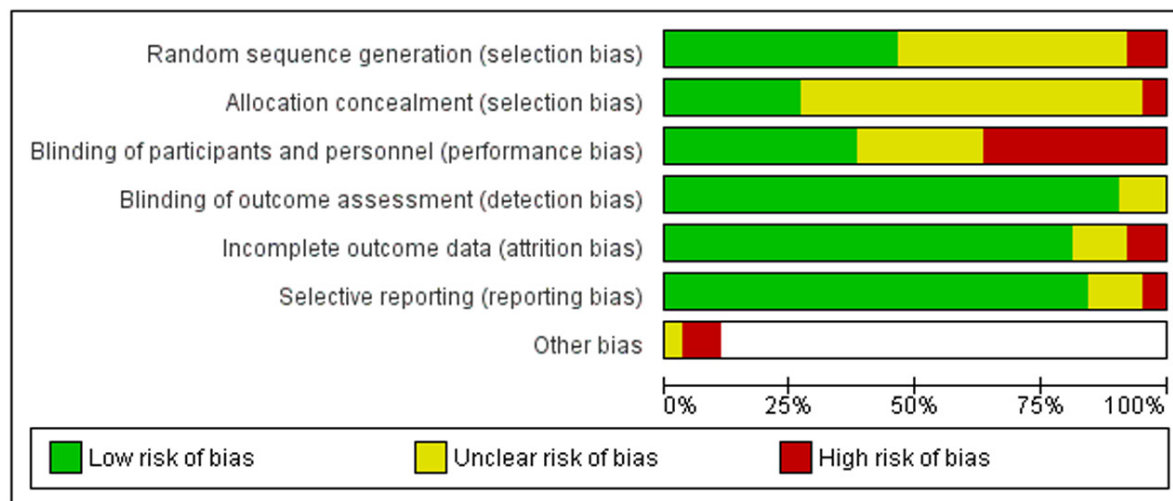
eNeura®
SPRING TMS®
Total Migraine System



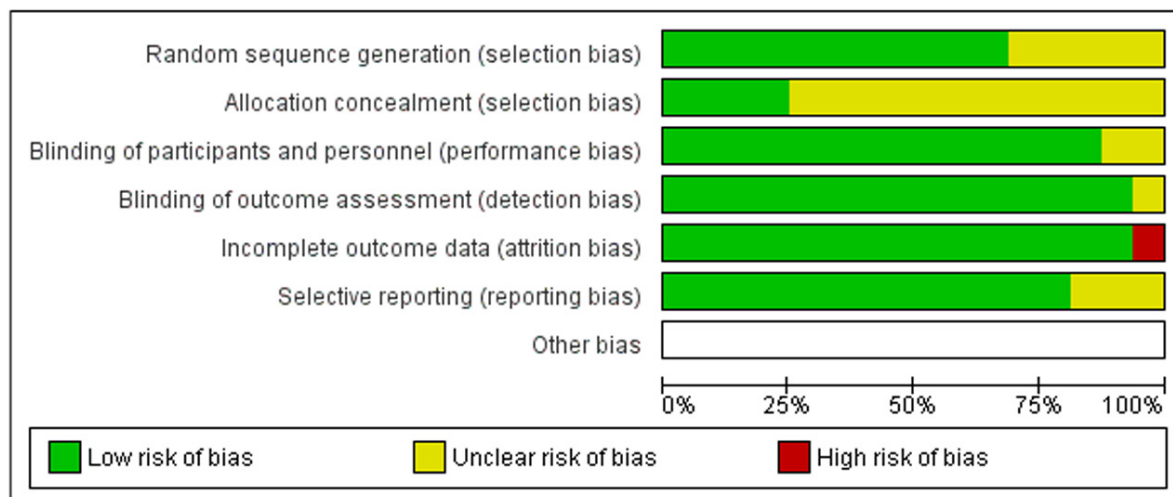
randomized, sham-controlled, parallel-group multi-session studies







Transcranial Magnetic Stimulation



Transcranial Direct Current Stimulation

Beyond MDD: Therapeutic Indications of Noninvasive Brain Stimulation

Indication	Year	Studies / Participants	Conclusions
Chronic Pain	2014	56 RCTs / N=1,710 (30 rTMS, 14 tDCS, 11 CES)	+ high-freq rTMS to M1 +/- tDCS; - CES
Chronic Pain in Spinal Cord Injury	2014	16 / N=616 (3 rTMS; 8 tDCS; 5 CES)	+/- tDCS - rTMS or CES
ALS	2013	3 RCTs / N=50	? rTMS
Stroke: UE Motor	2014	503 studies / N=18,078	Need large, robust RTCs
Stroke: ADL's	2013	15 studies / N=455	+/- tDCS (L/R/bilat DLPFC)
Stroke: Function	2013	19 trials / N=588	? rTMS
Stroke: Aphasia	2013	5 studies / N=54	(+) cathodal non-lesioned
Stroke: Dysphagia	2012	33 studies / N=6,779	Behavioral interventions; acupuncture; pharyngeal stim
MS: Spasticity	2013	9 RCTs / N=301	'low evidence' rTMS
Tinnitus	2011	5 trials / N=233	(+) low freq rTMS



Clinical Program – Approved Indications

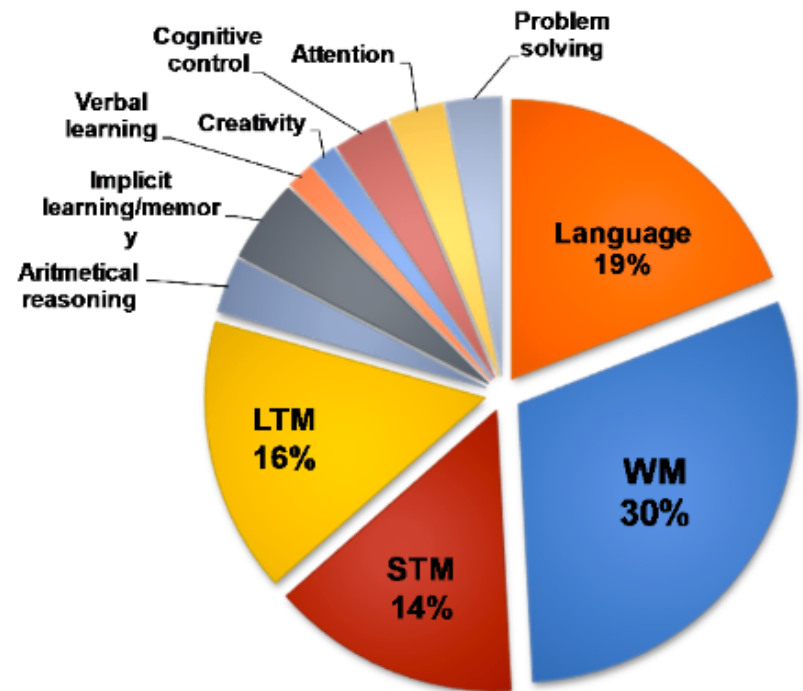
- Medication-resistant depression
- Stroke recovery (motor, non-fluent aphasia)
- Neuropathic pain
- Focal epilepsy

- Parkinson's disease (motor, mood, cognition)
- Hallucinations
- Tinnitus
- Cognitive control / impulsivity
- Dementia (cognitive function)

Cognitive Enhancement with tDCS

(Coffman et al., 2014; Horvath et al., 2015)

- Executive functions
 - Set-shifting
 - Stop signal tasks
 - Stroop tasks
- Language
 - Grammatical learning
 - Lexical learning
 - Verbal fluency
 - Naming
- Attention
 - Selective attention
 - Spatial attention
- Learning
 - Motor learning
 - Procedural learning
 - Explicit learning
 - Numerical learning
- Memory
 - Digit-span recall
 - Verbal episodic memory
- Visual working memory
- N-back working memory
- Mental arithmetic
- Automaticity
- Picture viewing/rating
- Visual perception
- Multimodal perception
- Social cognition
- Problem-solving
- Mood
- Gambling based risk taking
- Rumination



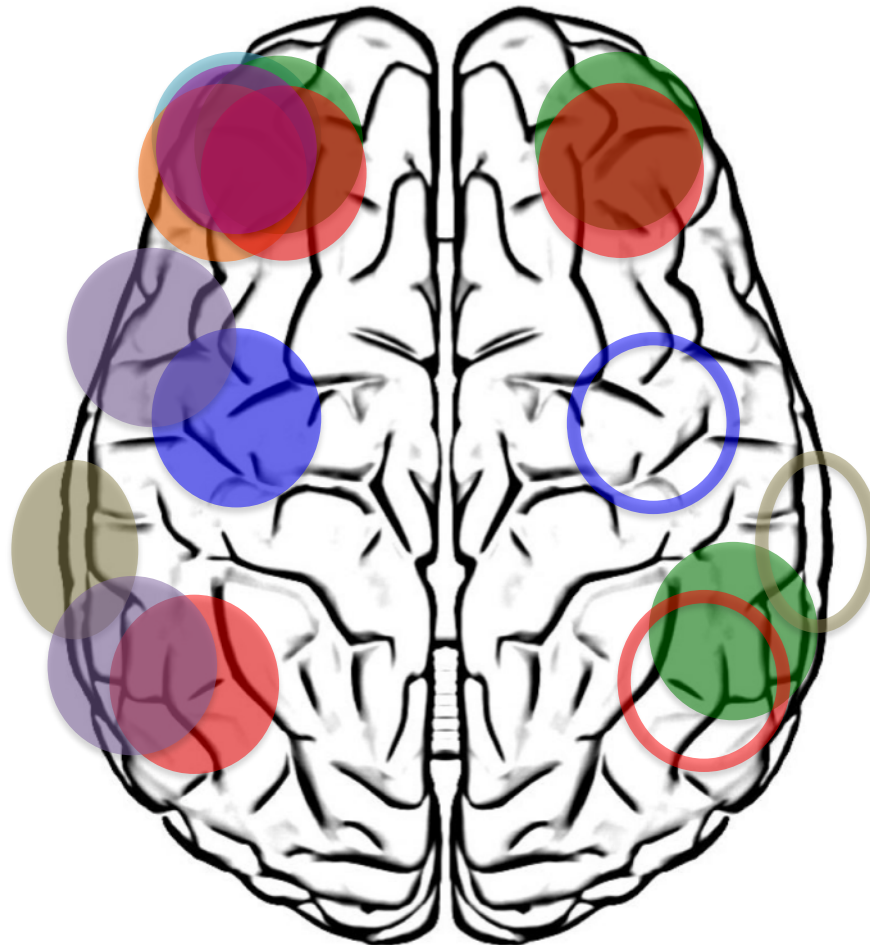
Cognitive Enhancement with tDCS: Stimulation Sites

Motor Learning

Probabilistic
Learning

Explicit Learning

Working
Memory



Attention

Social Cognition

Language

Complex
Cognition

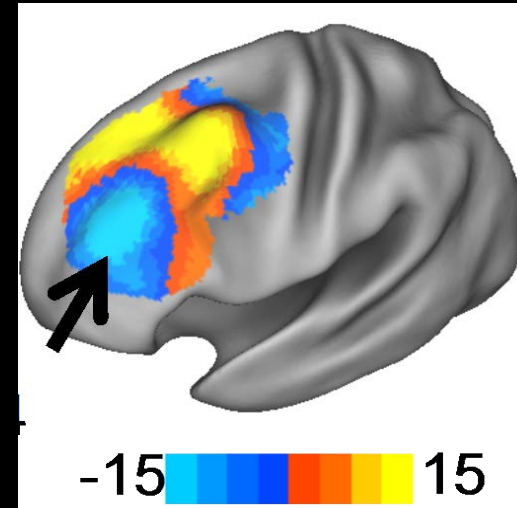
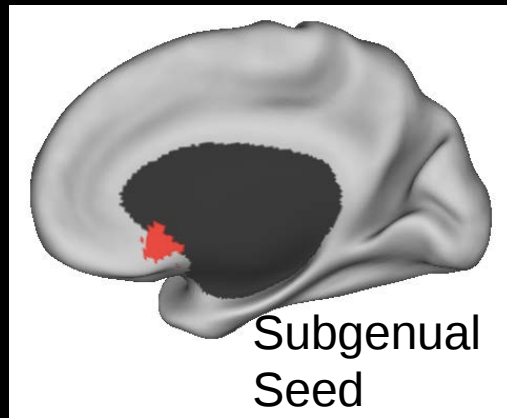
Therapeutic Uses of Noninvasive Brain Stimulation

1. Focus on Symptoms
2. Guide Intervention with Neuroimaging / Neurophysiology
 - MRI-guided for optimal spatial precision
 - EEG-guided for optimal frequency for given cortical location / condition

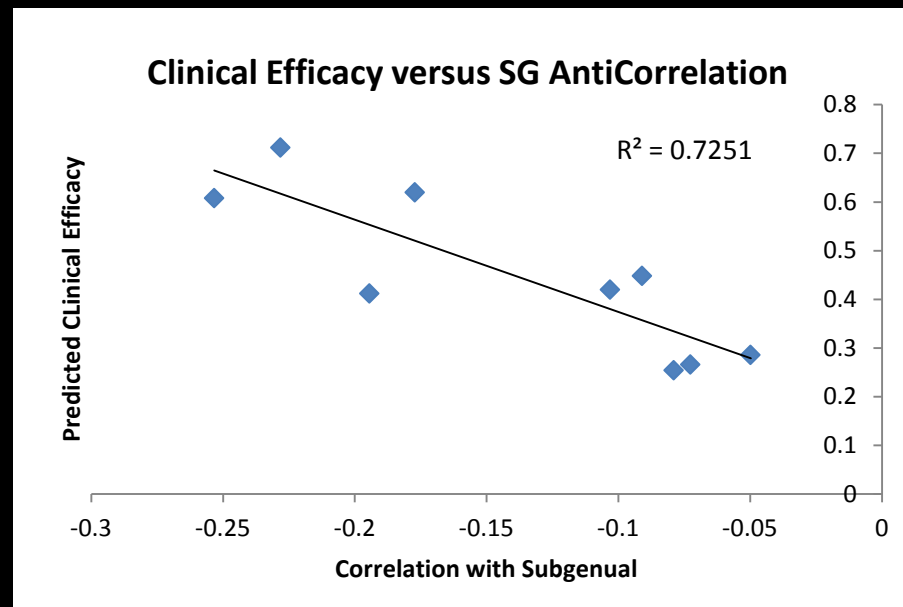


Mike Fox

Defining TMS target for depression



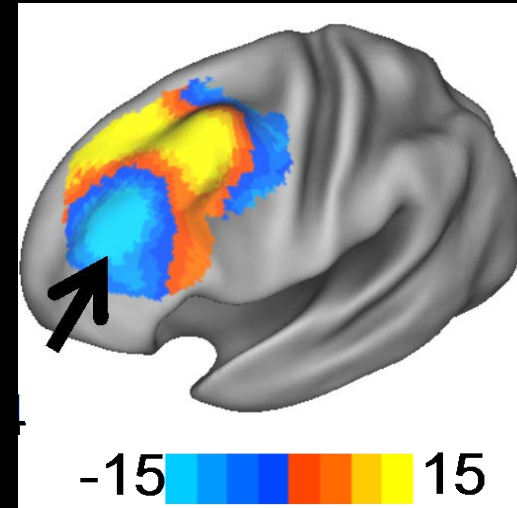
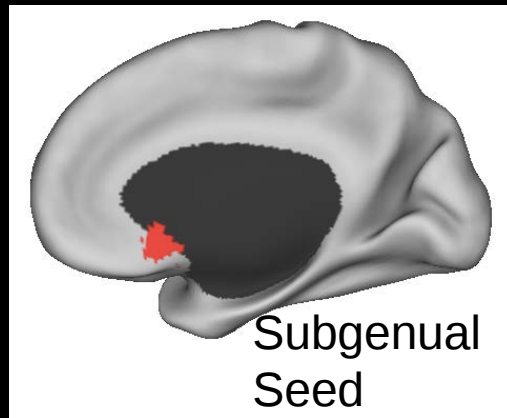
Group Map



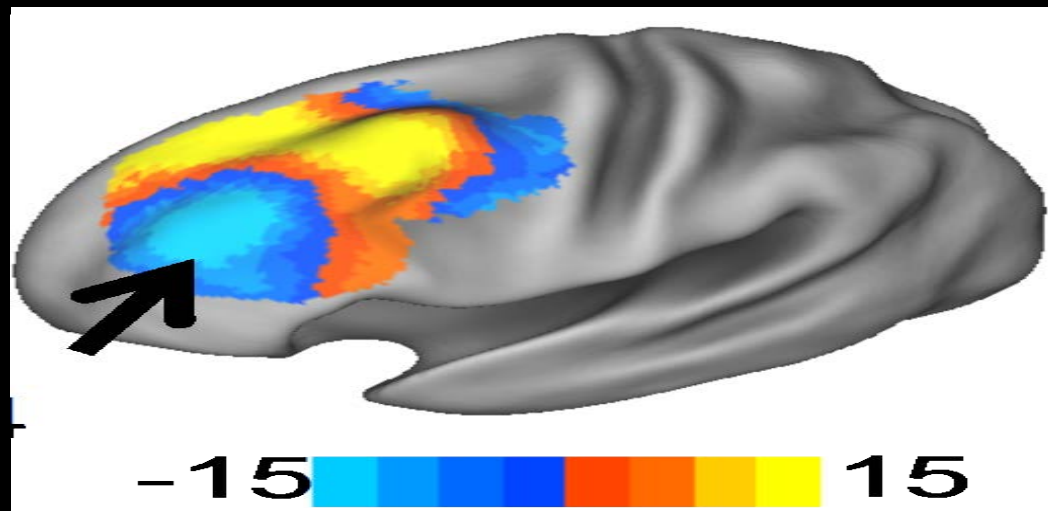


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Defining TMS target for depression



Group Map

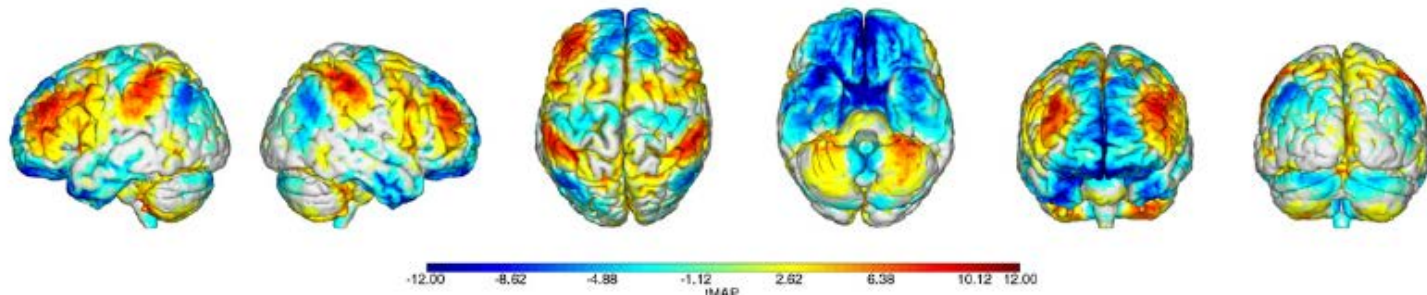


Subject 1

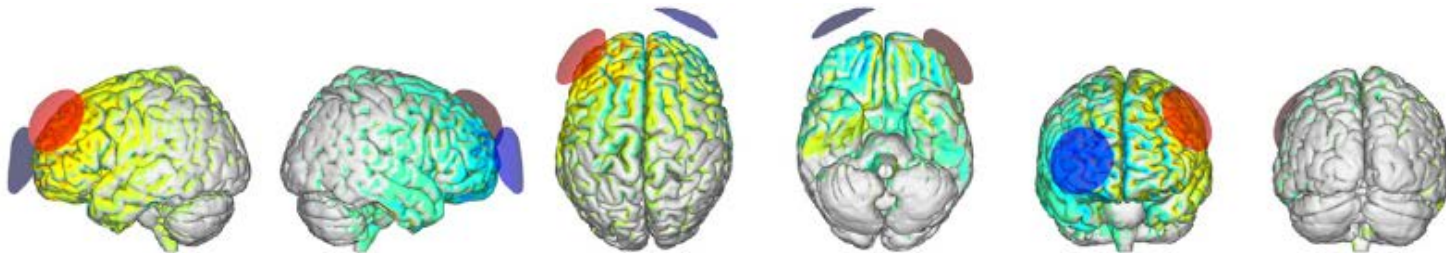
Subject 2

Multifocal, MRI-guided tCS

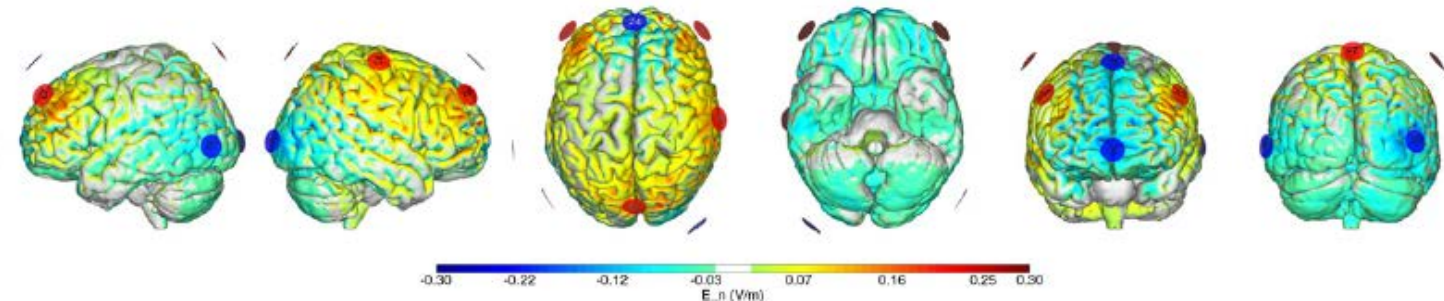
Fox et al PNAS 2014; Ruffini et al Neuroimage 2013



fMRI activation map



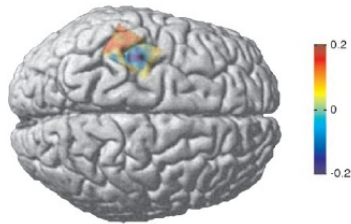
tCS solution with 2 electrodes



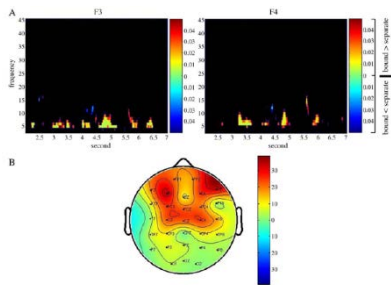
Multifocal tCS solution with 8 electrodes

Dominant Oscillations for Different brain regions

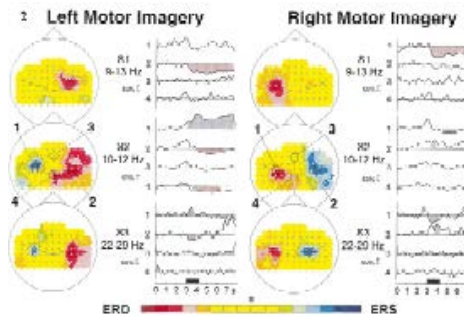
Alpha: automatic movements



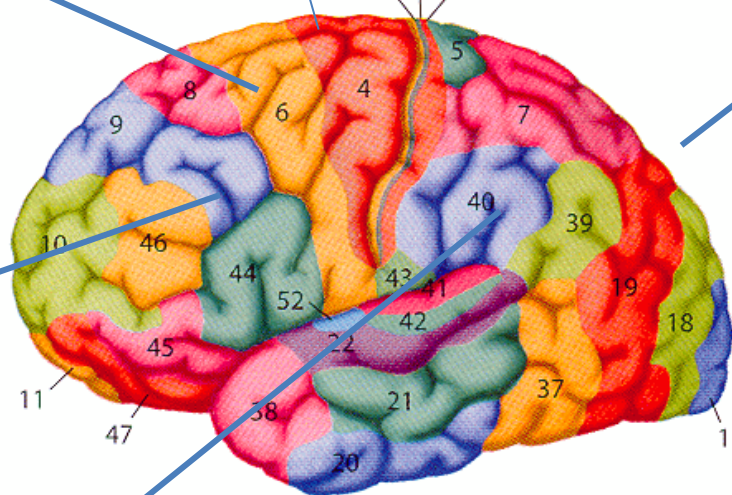
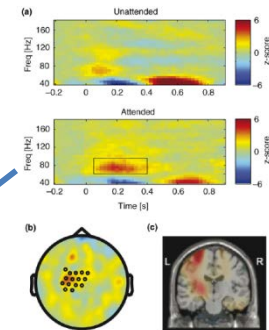
Θ : working /long-term memory



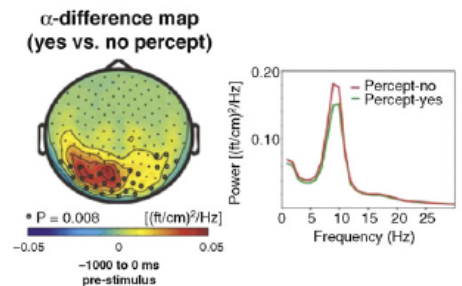
Beta: movement



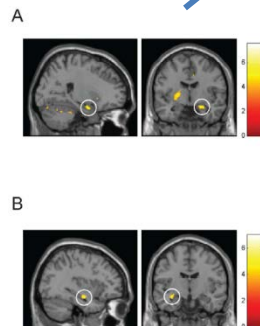
Gamma: selective attention



Alpha: visual perception

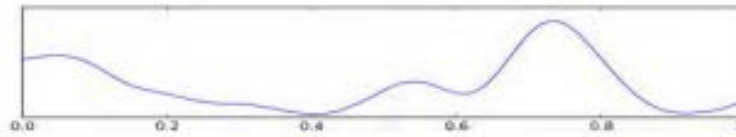


Θ : spatial orienting



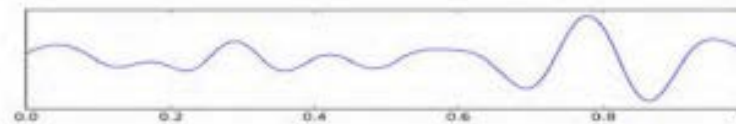
EEG Bands and Pathology

Delta (1 – 4 Hz)



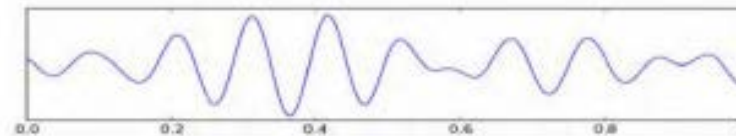
- Reduced synchrony in Schizophrenia
- Reduced amplitude in Alzheimer
- Increased Amplitude in Bipolar dis.

Theta (4 – 8 Hz)



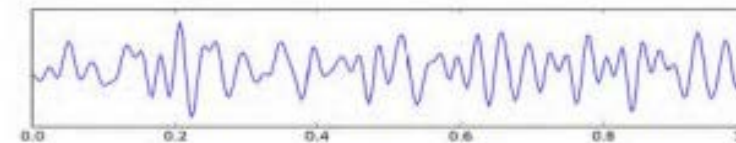
- Reduced synchrony in Schizophrenia
- Reduced synchrony in Alzheimer

Alpha (8 – 13 Hz)



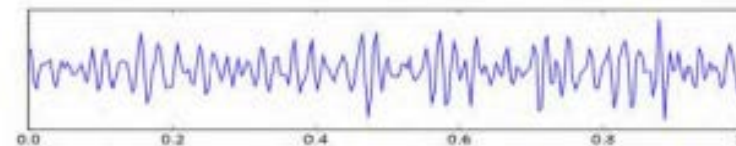
- Reduced coherence in Alzheimer
- Increased phase-locking at Frontal and Central electrodes in Schizophrenia

Beta (13 – 30 Hz)



- Reduced Coherence in Alzheimer and Schizophrenia
- Increased amplitude in Parkinson
- Increased Coherence in Bipolar dis.

Gamma (30 – 80 Hz)



- Decreased/increased amplitude in Schizophrenia (?)
- Increased Phase-locked response in ADHD

Therapeutic Uses of Noninvasive Brain Stimulation

1. Focus on Symptoms
2. Guide Intervention with Neuroimaging / Neurophysiology
 - MRI-guided for optimal spatial precision
 - EEG-guided for optimal frequency for given cortical location / condition
3. Consider Needs of Special Populations (e.g. pediatrics)
4. Combine with Behavioral / Pharmacologic / Other Interventions

Alzheimer's Disease

Concurrent TMS stimulation with Cognitive Training



Therapeutic Uses of Noninvasive Brain Stimulation

On-Label	Off-Label	Clinical Trial
Major Depressive Disorder	Malpractice coverage Informed consent	IRB Informed consent
rTMS - Neuronetics - Brainsway	FDA Cleared Device - TMS - tDCS: iontophoresis <i>[not tACS or tRNS]</i>	IDE ?
	Regulation - Advertise - Billing	Trial registration
	Stroke: UE Motor	Funding

Home Use
Patient Initiated - Do-it-yourself devices - Purchased devices
Consumer (non-medical) devices

Rationale

Brittain et al., Curr. Bio 2013

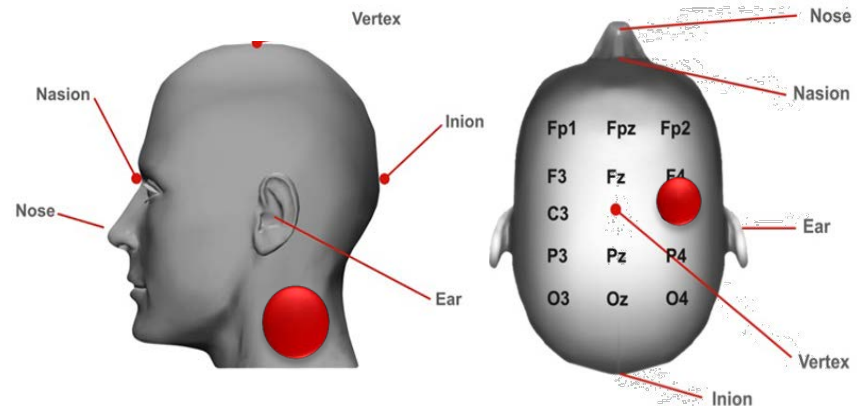
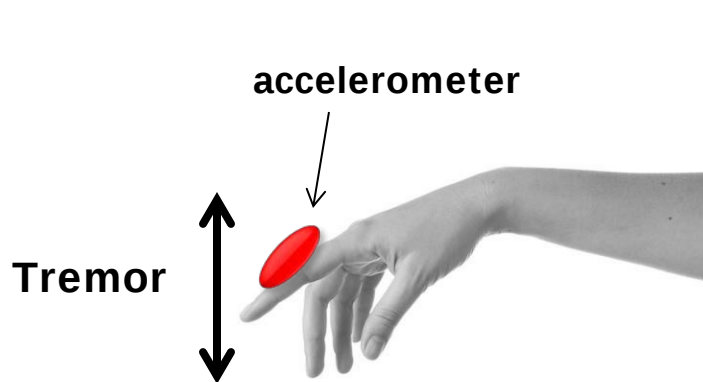
- Can tACS reduce tremor in PD patients?

Design

Closed-loop tACS – tremor phase (accelerometer)

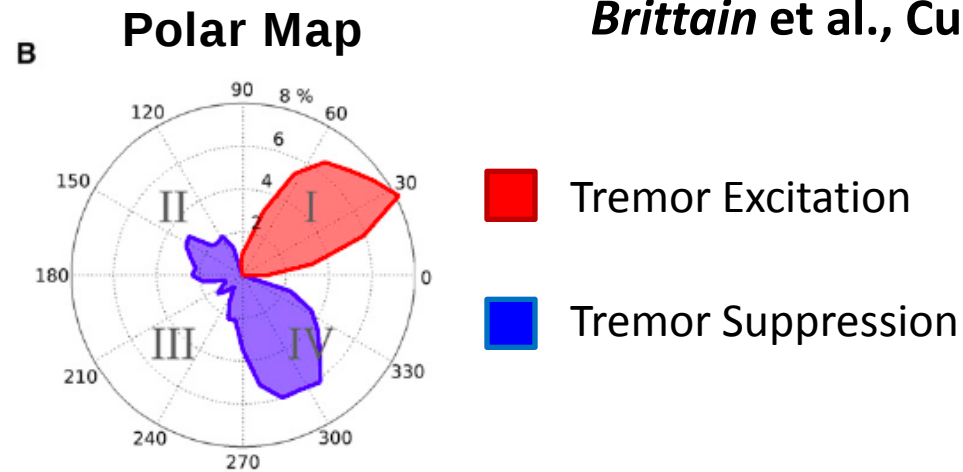
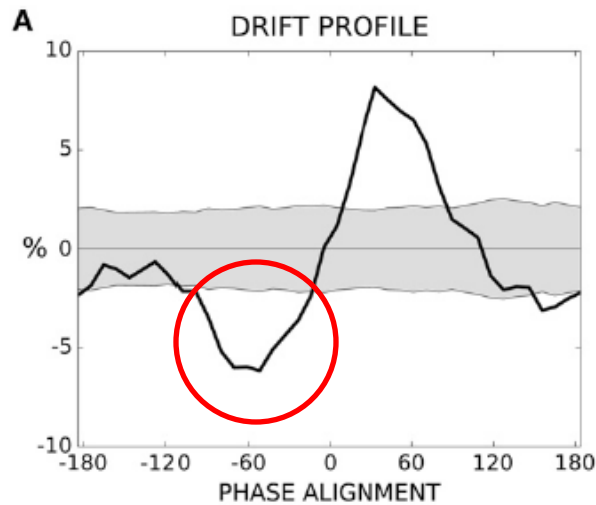


Tremor amplitude (accelerometer)

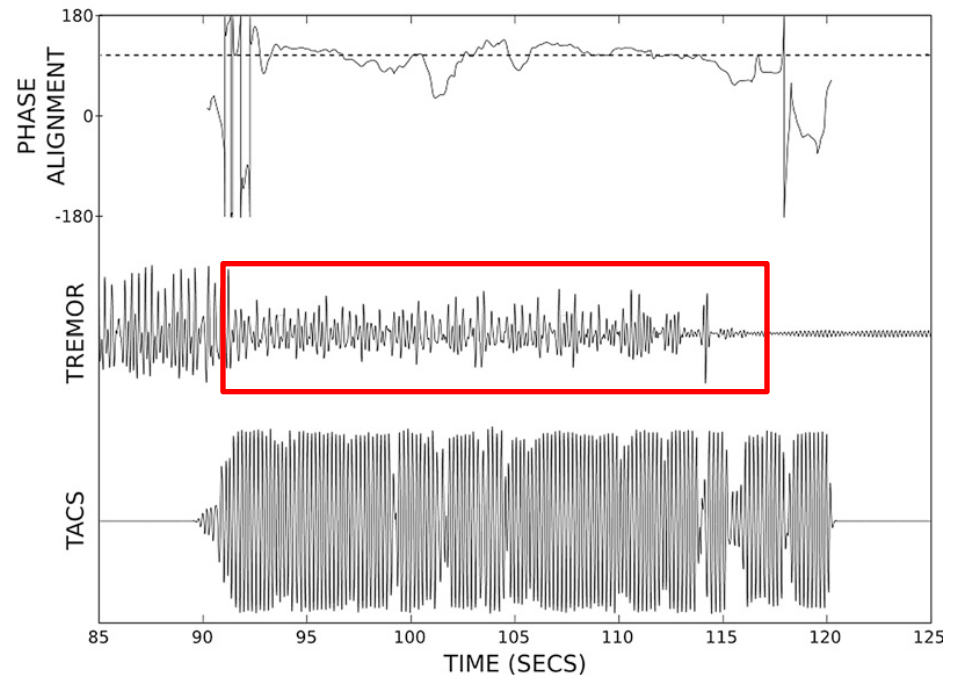


Tremor Suppression?

Brittain et al., Curr. Bio 2013



Identification of the optimal
Phase-Delay for tremor
suppression



Phased-locked tACS reduced tremor by up to 50%