Non-invasive brain stimulation in Tourette syndrome and OCD: why is it relevant? how are we investigating it in Alberta?

Dr. Davide Martino, PhD MD

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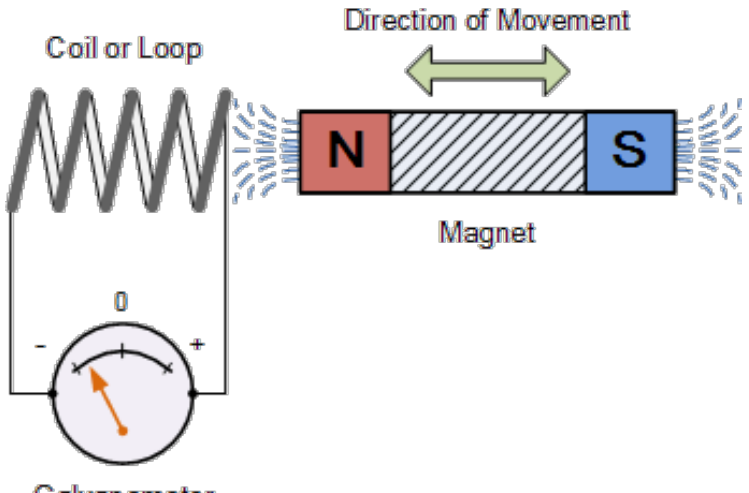
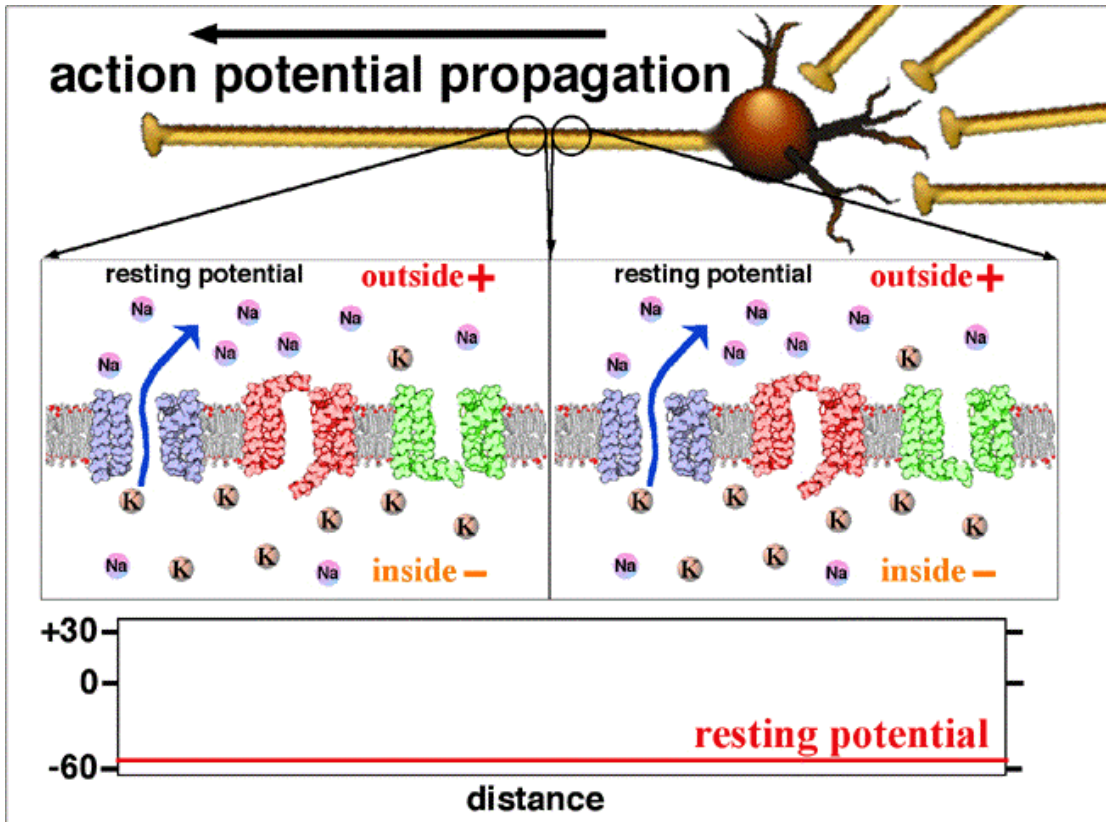
UNIVERSITY OF CALGARY

CLINICAL NEURO SCIENCES
CALGARY CANADA

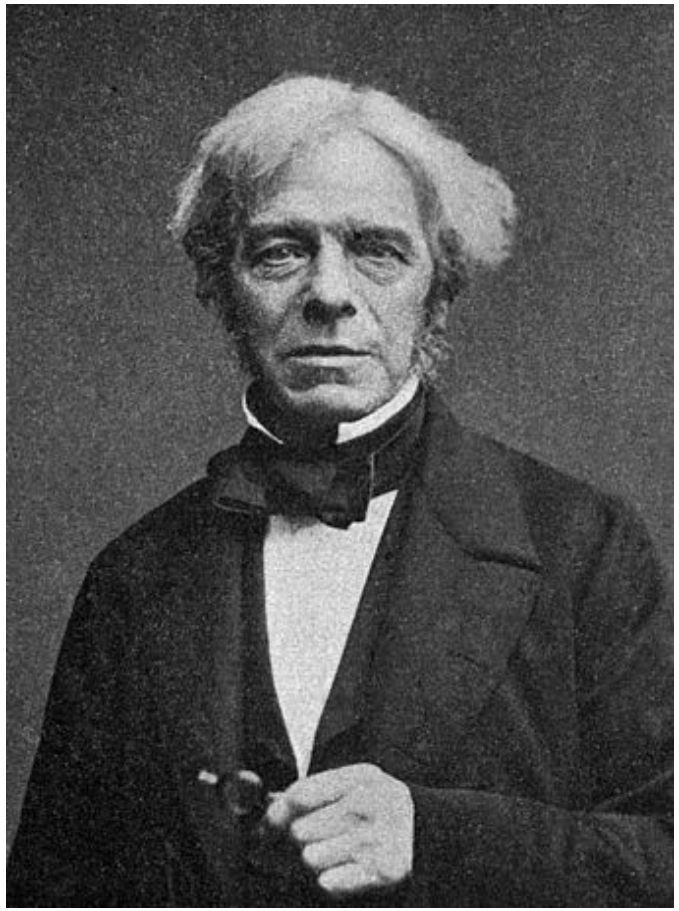
HOTCHKISS BRAIN INSTITUTE

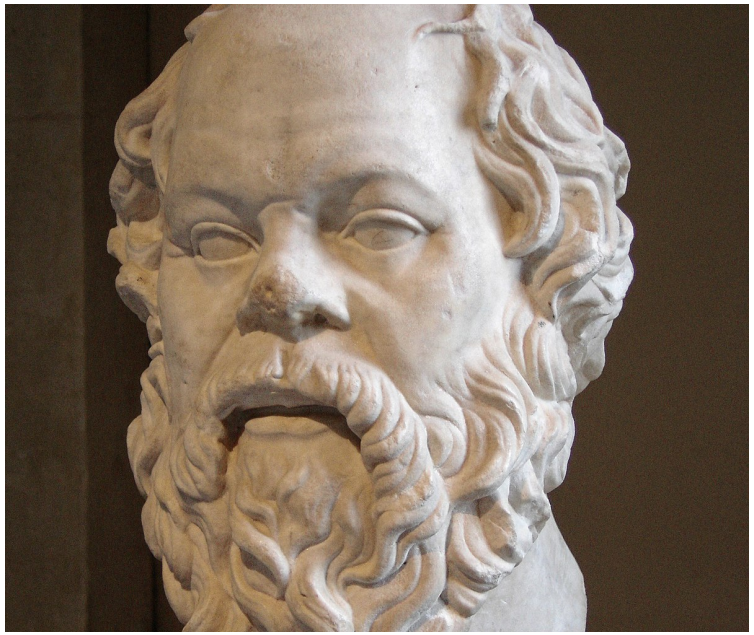
N3
Non-invasive Neurostimulation Network





MICHAEL FARADAY
1831:
Electromagnetic induction





Fifth dynasty of Egypt:

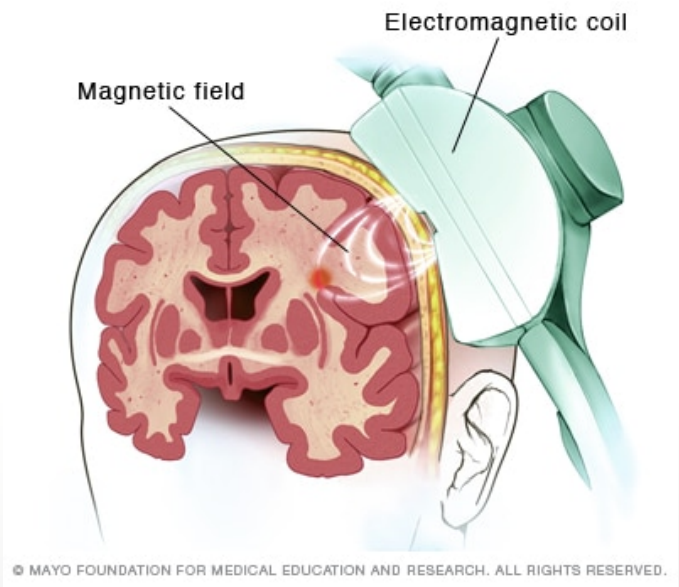
early 25th century BC

until the mid 24th century BC

Fifth century BC

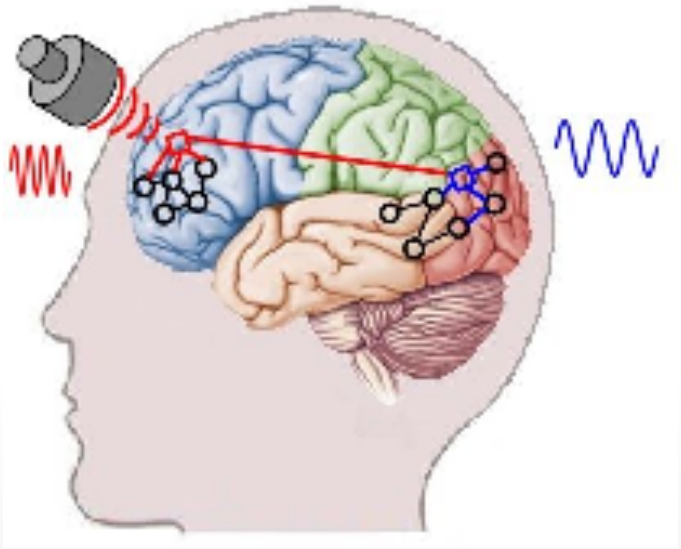
during the time of Socrates

TMS



Transcranial magnetic stimulation

FUS

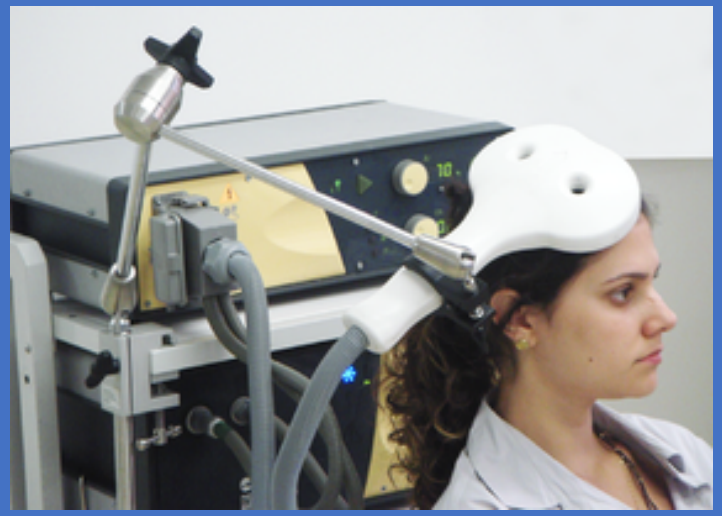


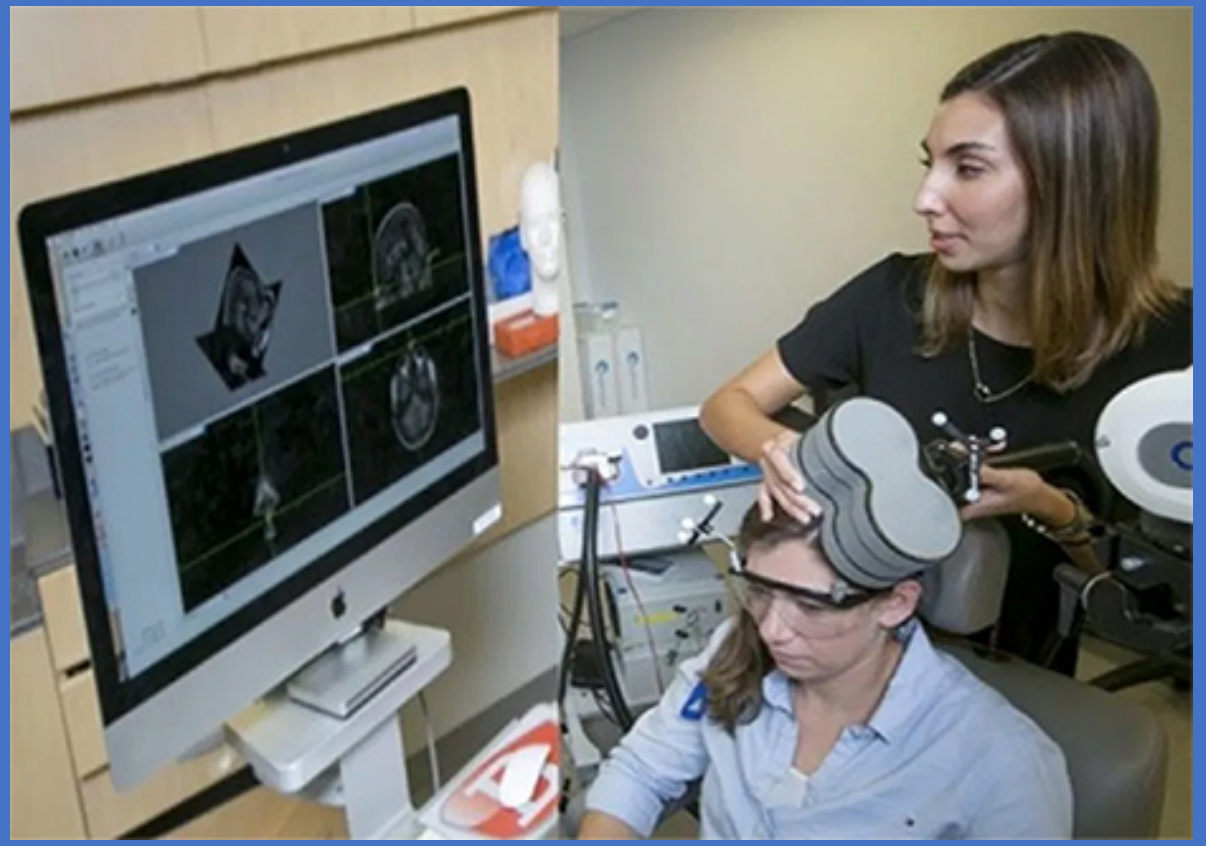
Focused ultrasound stimulation

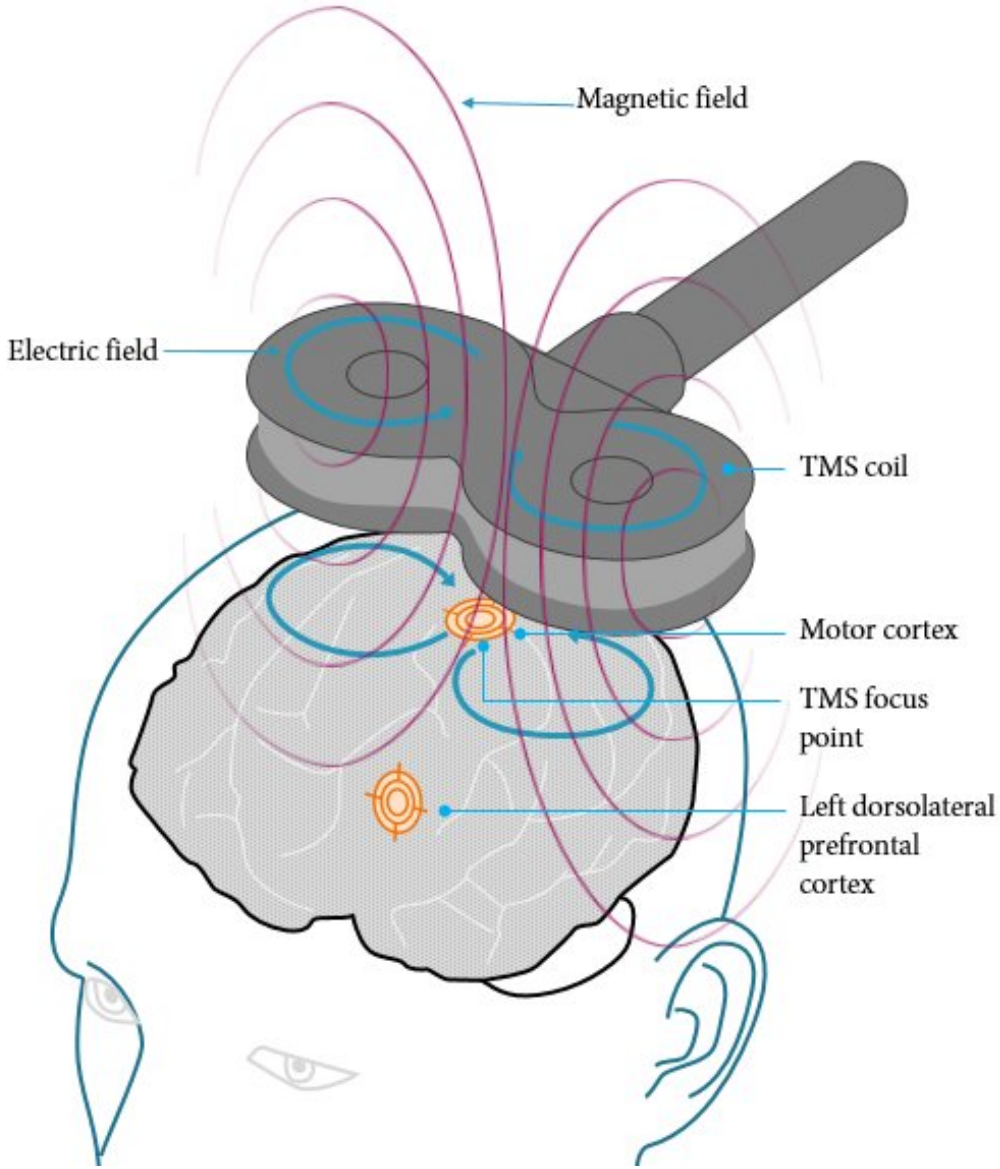
tCS

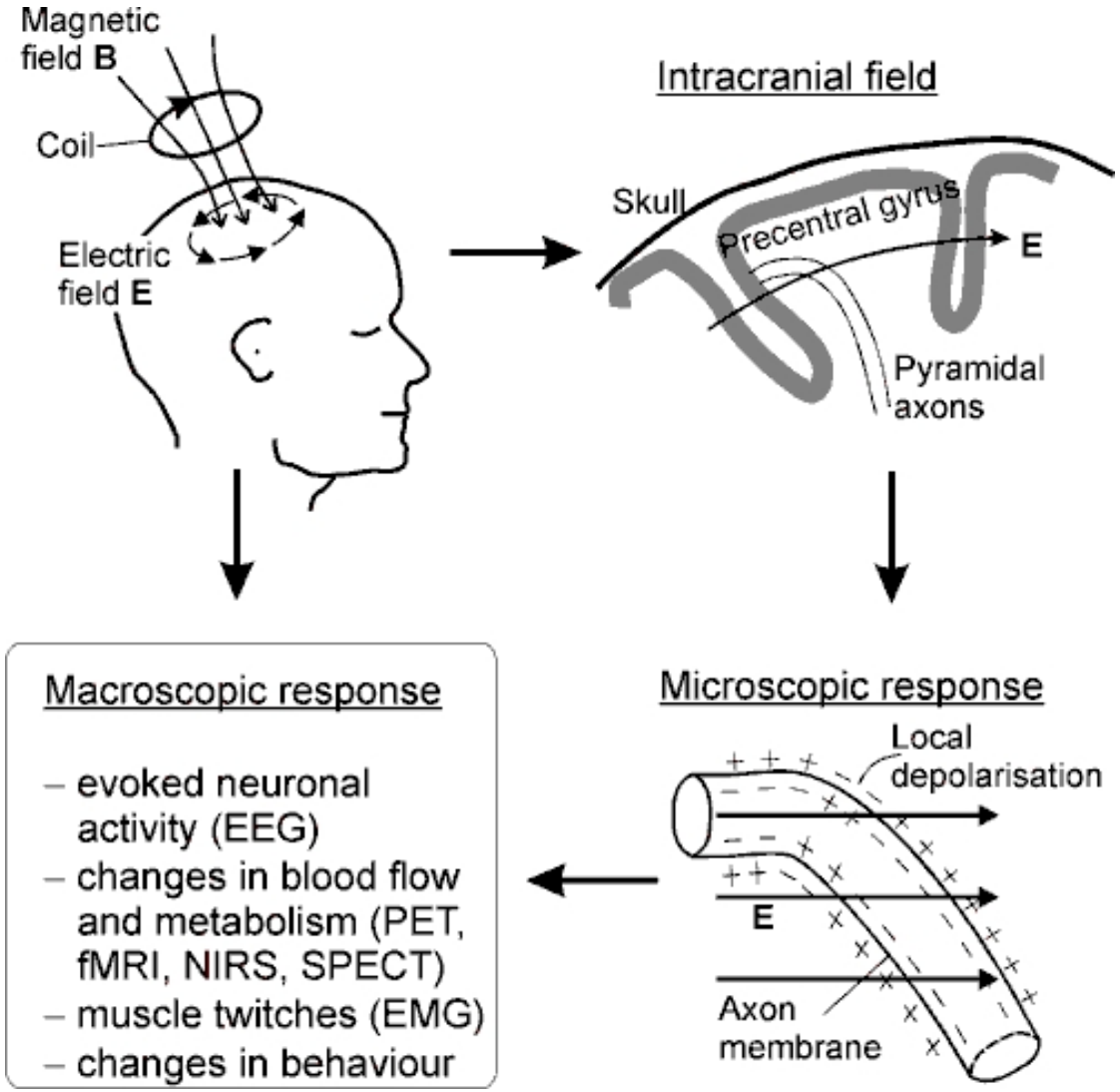
Transcranial current stimulation

NEURONAVIGATION PROCEDURE
USING MAGNETIC RESONANCE IMAGING

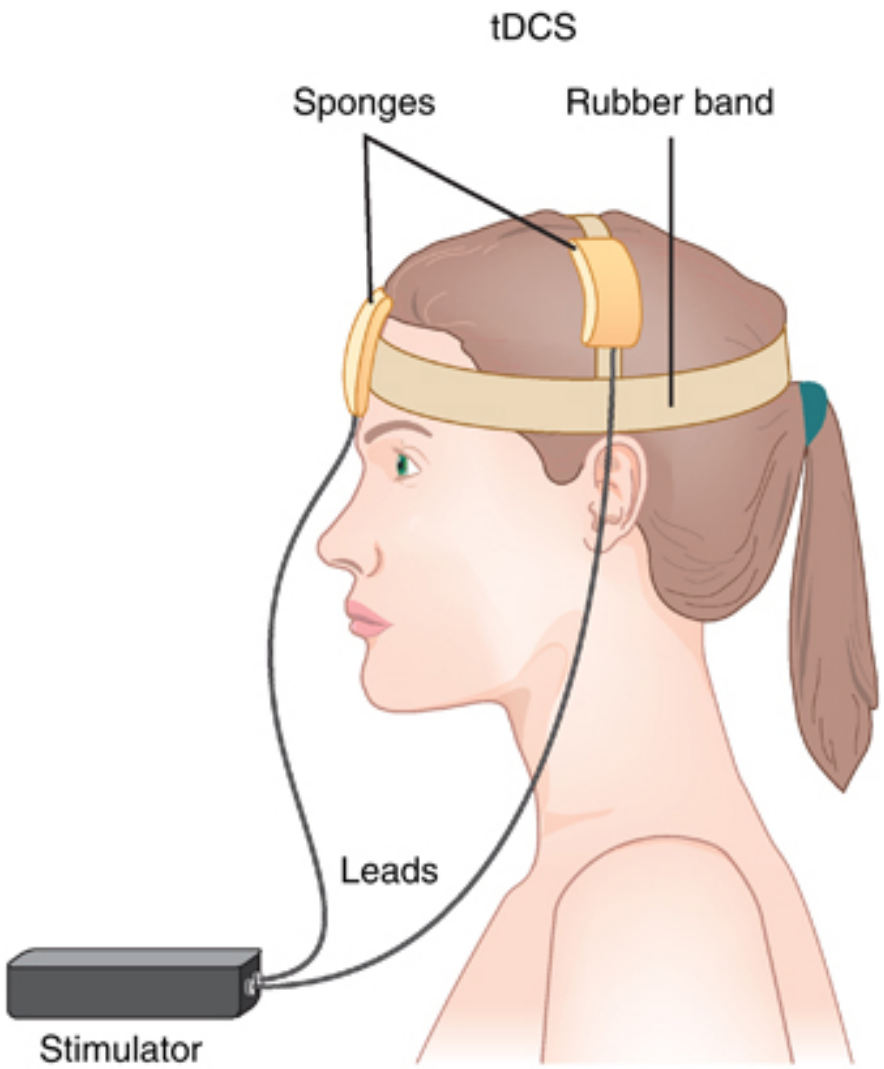






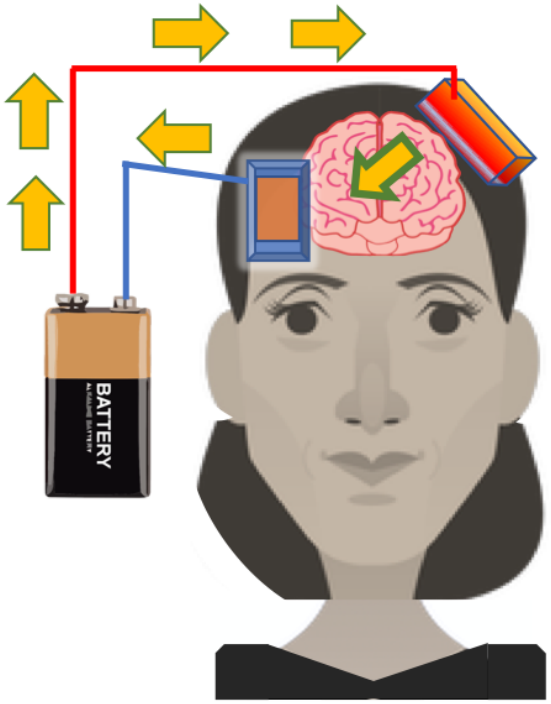


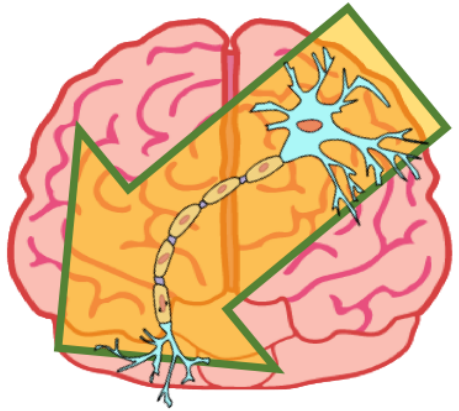
HIGH FREQ → EXCITATORY
LOW FREQ → INHIBITORY
VERY HIGH FREQ → theta burst → longer PLASTICITY effects



1 Direction of current flow from device across head and brain

transcranial
Direct
Current
Stimulation

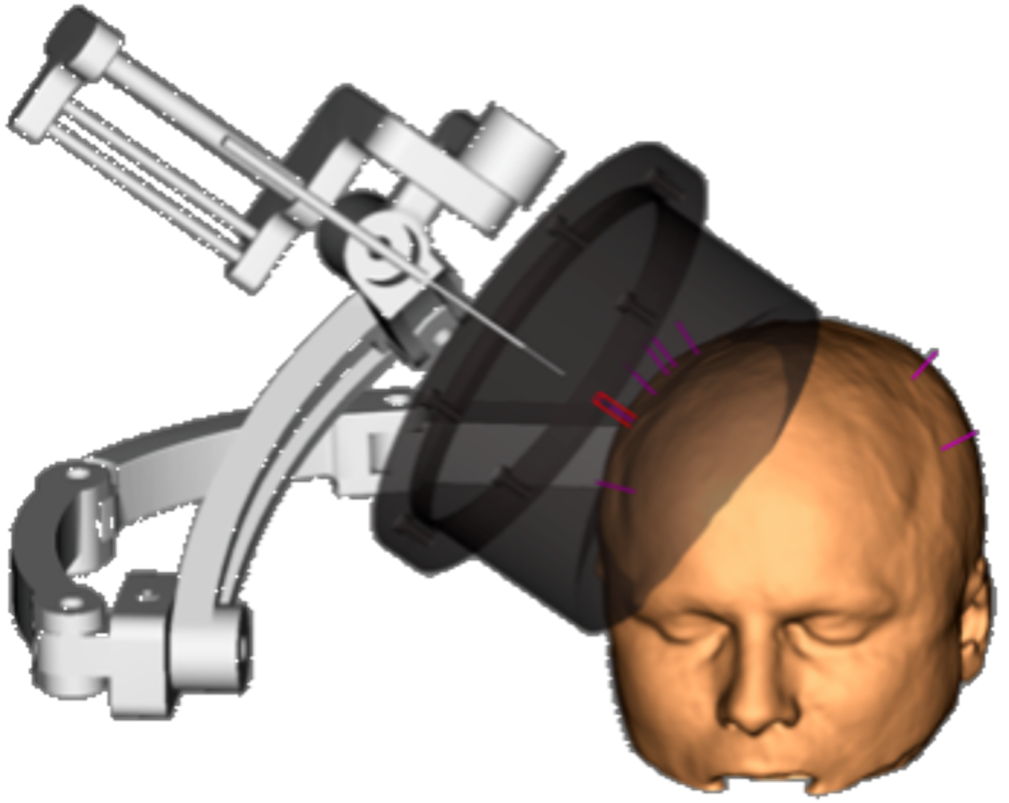




2 Modulation of brain cells (neurons) by current flow

ANODAL→ EXCITABILITY-INCREASING

CATHODAL→ EXCITABILITY-DECREASING



MRI-GUIDED LOW INTENSITY, LOW FREQUENCY FOCUSED ULTRASOUND STIMULATION

Enhancement and Treatment

Treatment → restoration of functioning

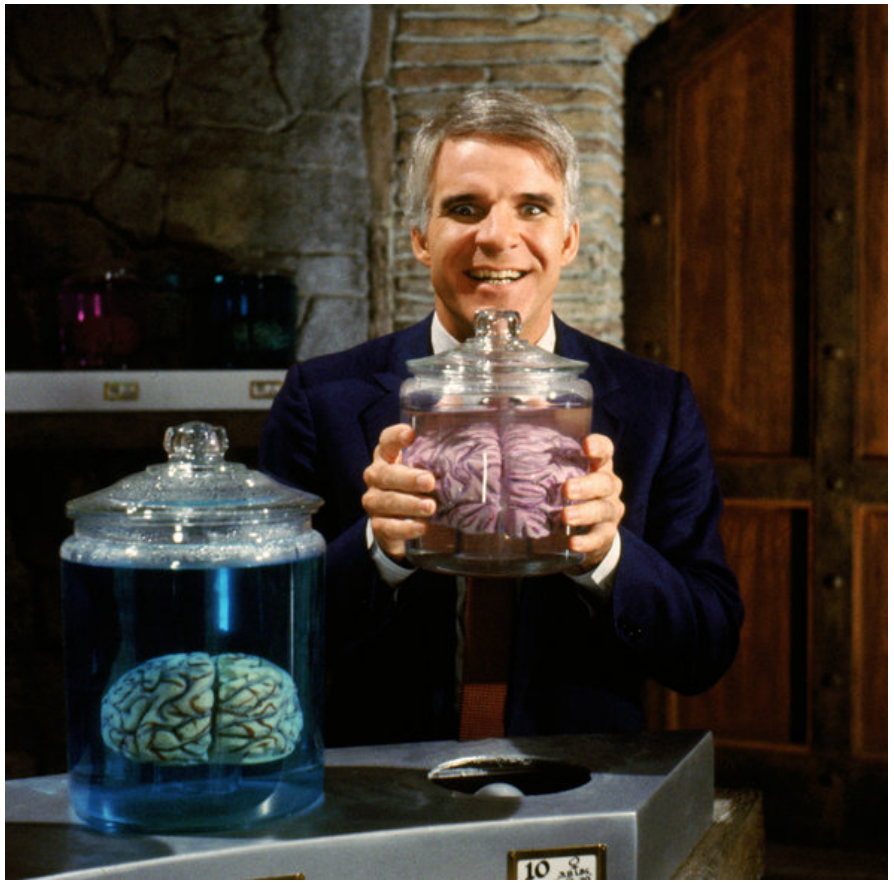
Enhancement → improving »normal« functioning

The New York Times

The Opinion Pages
Op-Talk
Opinions From All Over

This Procedure May Improve Your Brain — and Uncover the Real You

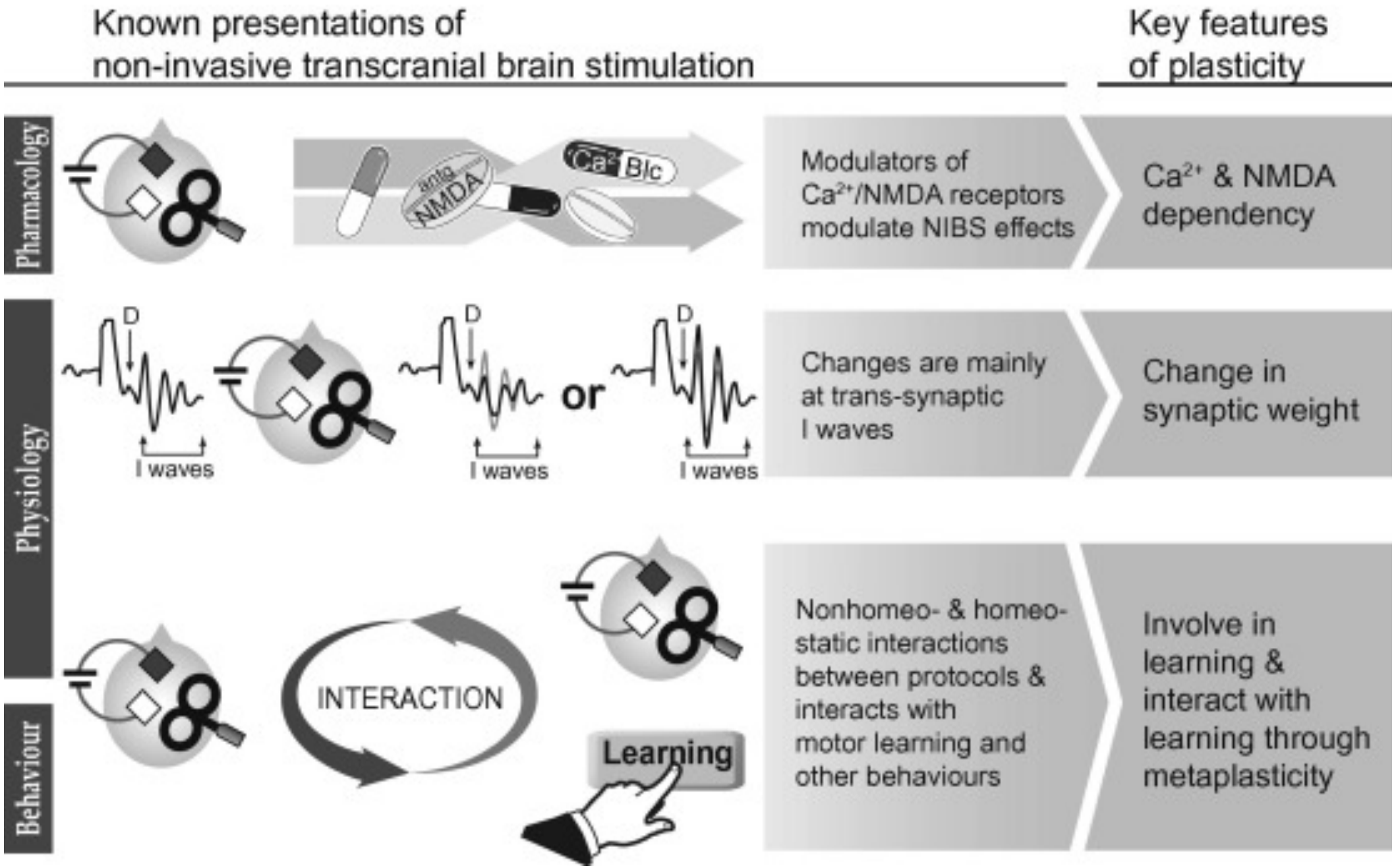
By Anna Altman July 17, 2014 5:41 pm



"What role does doubt and fear play in our lives if its eradication actually causes so many improvements? Do we make more ethical decisions when we listen to our inner voices of self-doubt or when we're freed from them? If we all wore these caps, would the world be a better place?"

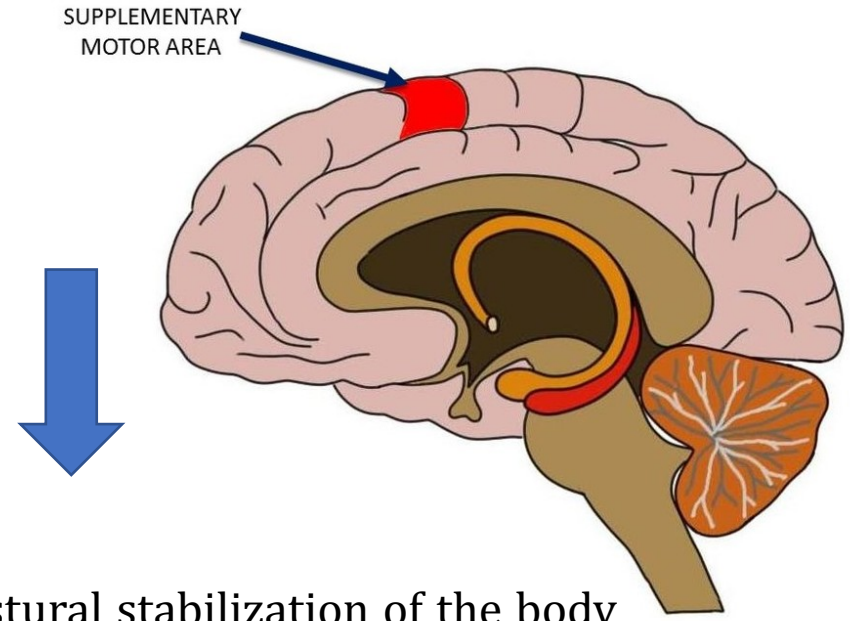
"Is brain boosting a fair addition to the cognitive enhancement arms race? Will it create a Morlock/Eloi-like social divide where the rich can afford to be smarter and leave everyone else behind? Will Tiger Moms force their lazy kids to strap on a zappity helmet during piano practice?"

[Sally Adee, scientific journalist]



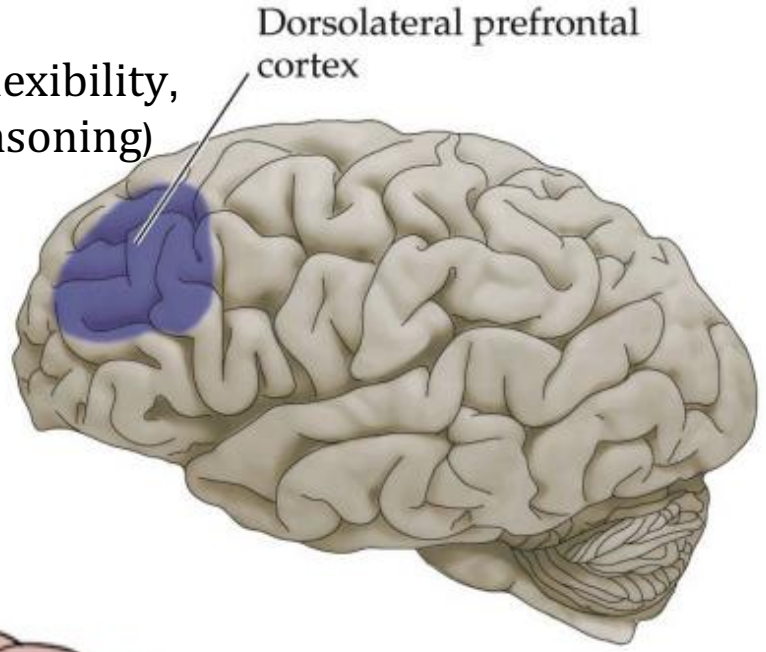
Huang YZ…Rothwell J, *Clin Neurophysiol* 2017

rTMS in OCD

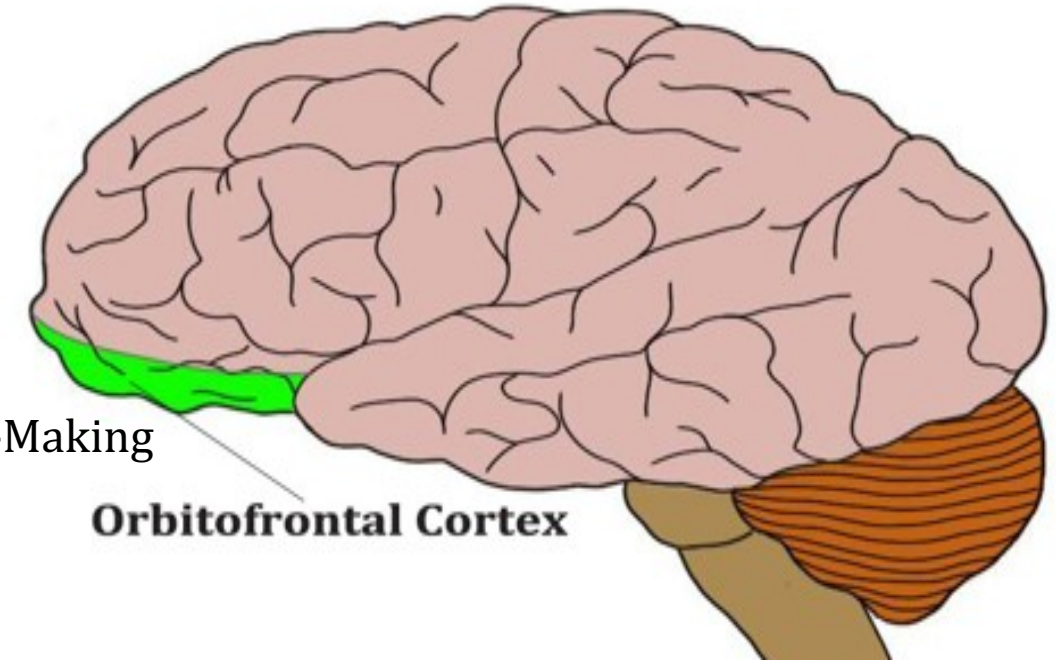


Postural stabilization of the body
Coordination of both sides of the body (e.g. during bimanual action)
Control of movements that are internally generated rather than triggered by sensory events
Control of sequences of movements

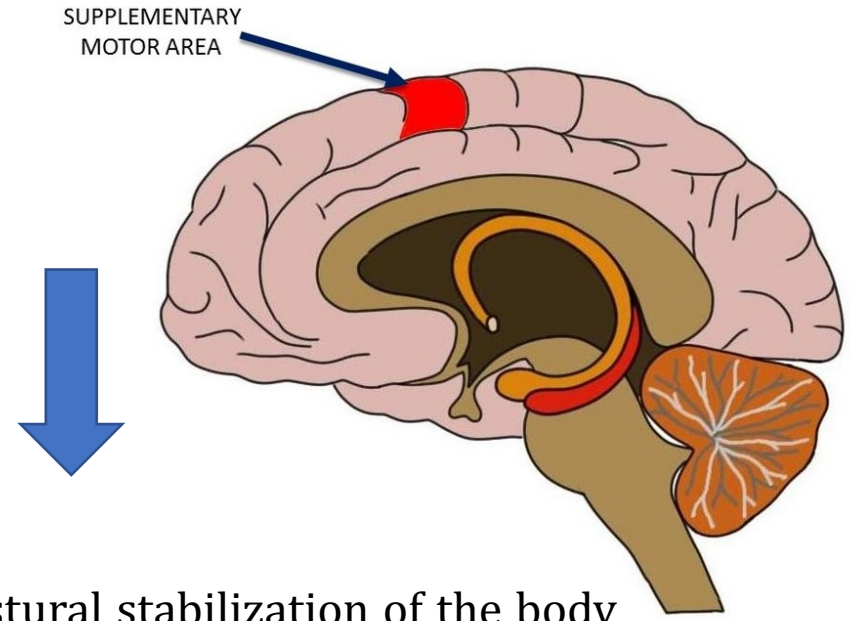
Executive functions (WM, cogn flexibility, planning, inhibition, abstract reasoning)
Highest level of motor planning, organization and regulation



Emotion and Reward in Decision-Making



tDCS in OCD



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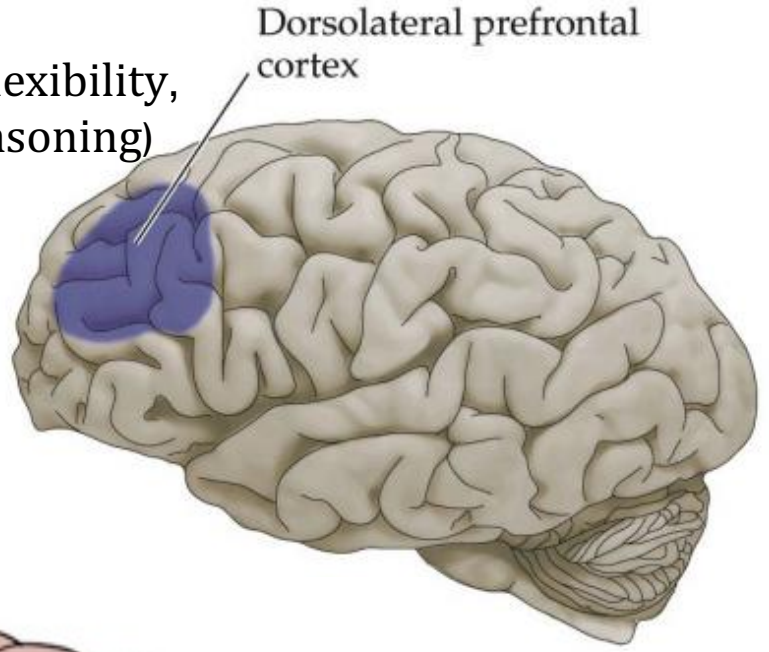
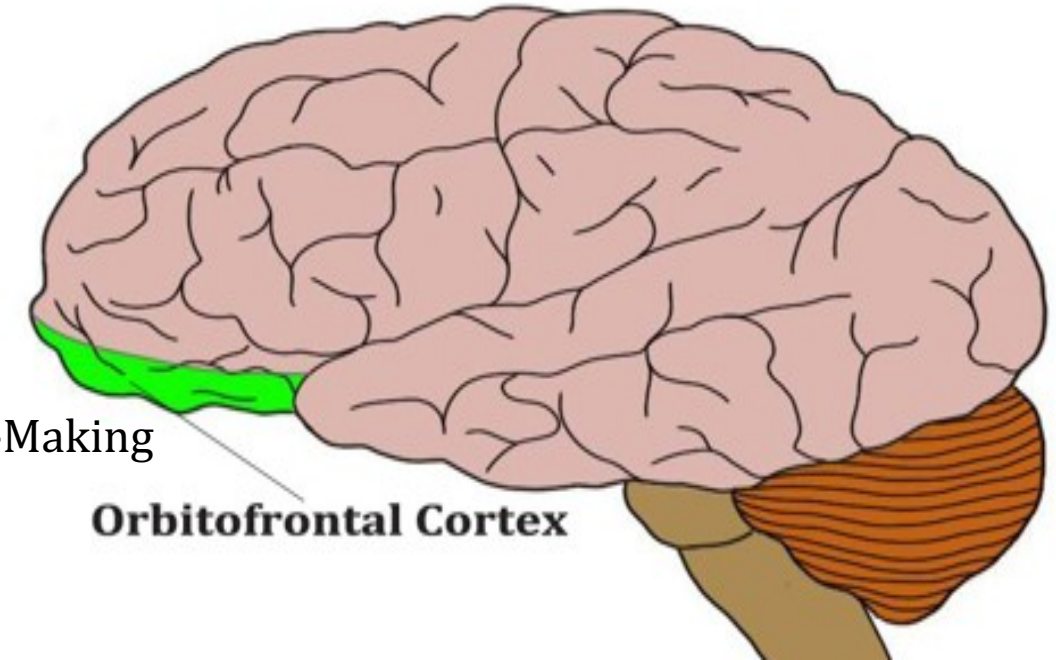
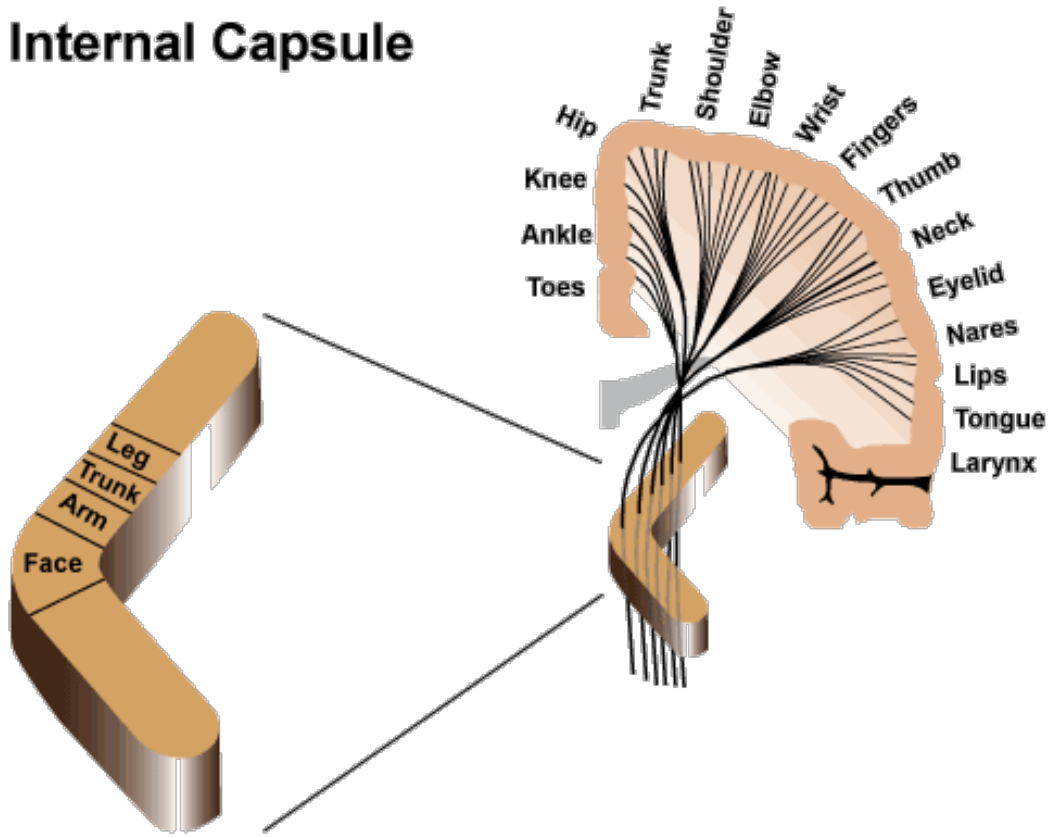
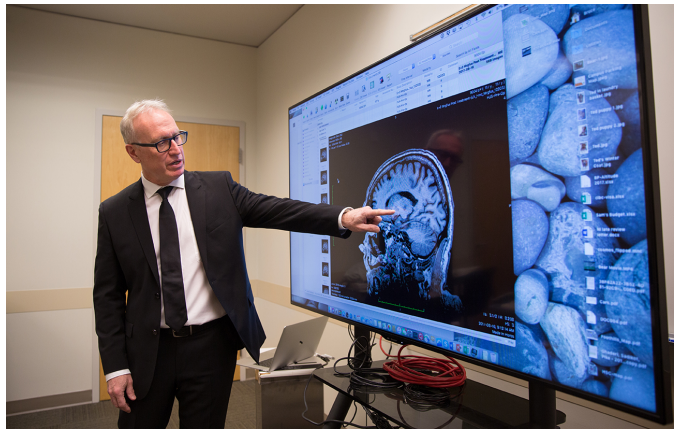


Emotion and Reward in Decision-Making



MRI-GUIDED HIGH INTENSITY
FOCUSED ULTRASOUND STIMULATION = invasive procedure

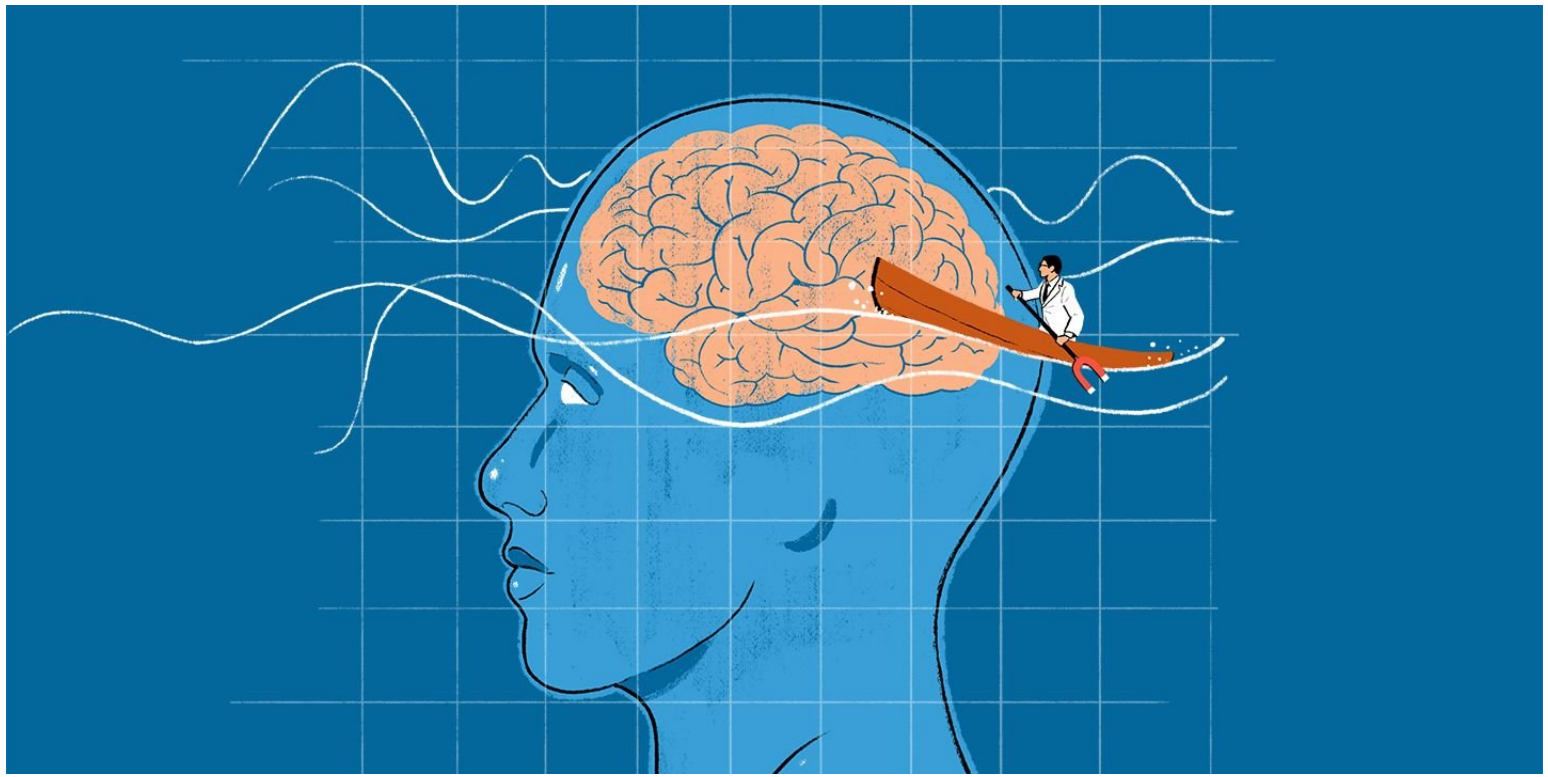




Surgery without opening the skull
Focused energy into a very small spot

Ongoing study for adults aged 21-65 with refractory OCD

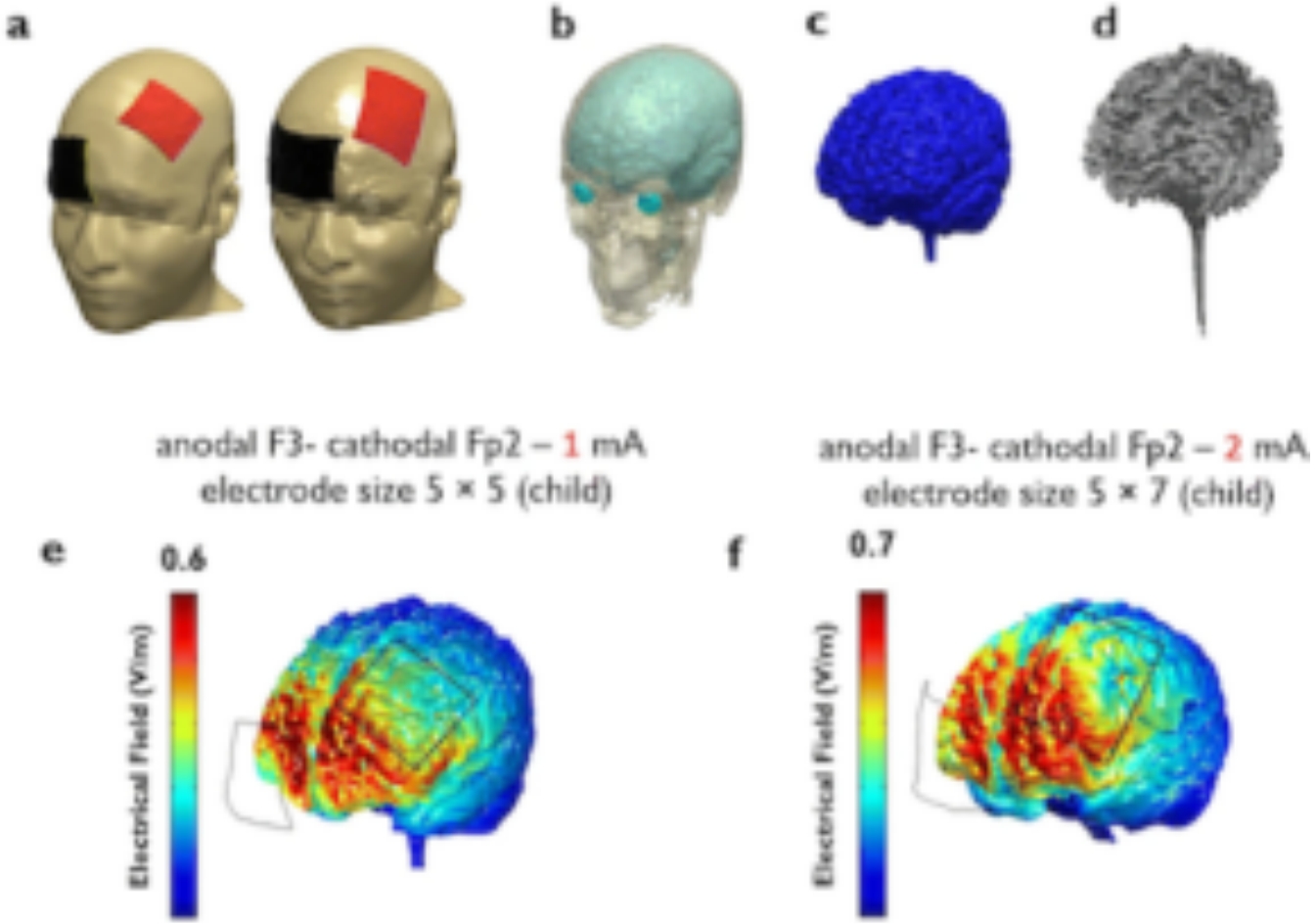
rTMS in ADHD



No clear evidence of efficacy

Future investigations of either low frequency or high frequency rTMS on ADHD is required

tDCS in ADHD

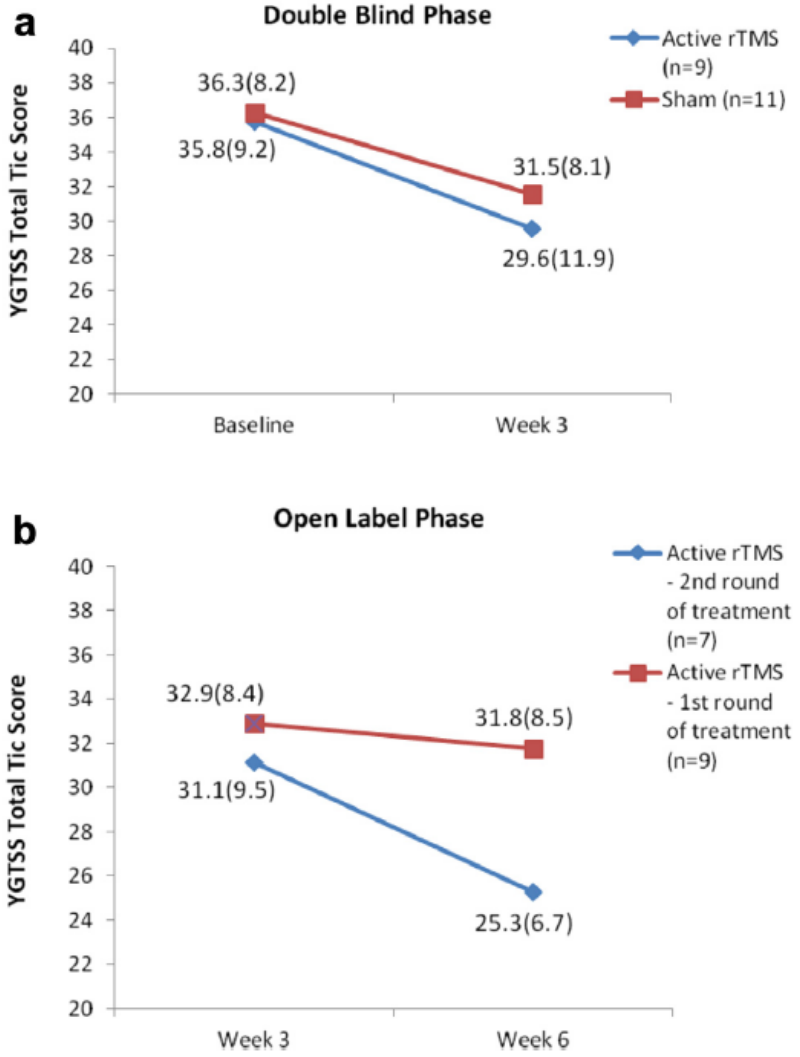


Partial improvement of symptoms and cognitive deficits

ANODAL tDCS over the dlPFC: superior effect

Optimization of the stimulation parameters to improve clinical efficacy

DB-RCT of low-frequency (1 Hz) bilateral rTMS of SMA



Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

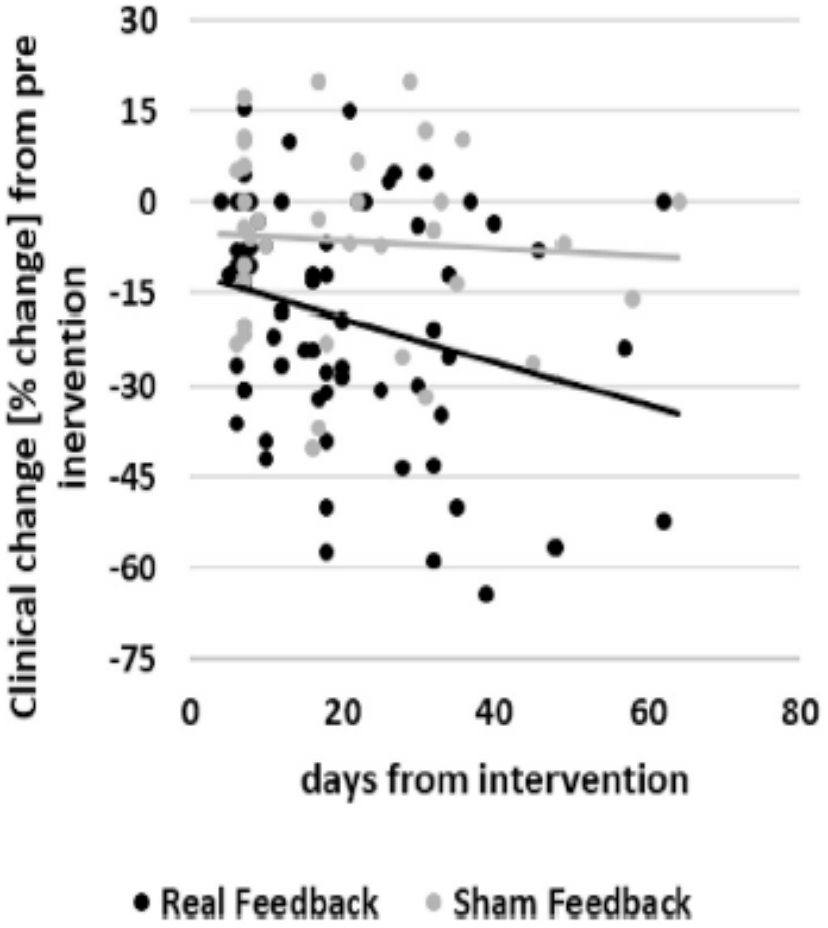
Original Research

Randomized Sham Controlled Double-blind Trial of Repetitive Transcranial Magnetic Stimulation for Adults With Severe Tourette Syndrome

Angeli Landeros-Weisenberger[a,1], Antonio Mantovani[b,c,1], Maria G. Motlagh[a,d,1], Pedro Gomes de Alvarenga[e], Liliya Katsovich[a], James F. Leckman[a,*], Sarah H. Lisanby[f]

- **Supplementary motor area →** favourite target from uncontrolled observations [metaanalysis from Hsu et al., *Brain Stimul* 2018]
- **2 RCTs of inhibitory TMS**
  - 1 with 30 Hz cTBS at 90% RMT
  - 1 with 1 Hz rTMS
- **Superiority to placebo not confirmed**
  - BUT, rTMS → significant reduction of tic severity decrease compared to baseline at end of post-randomization phase in pts randomized to active arm

Real time fMRI-neurofeedback



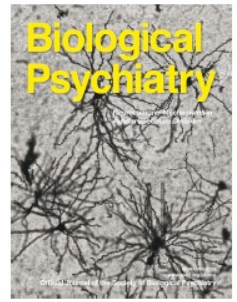
Time course of clinical change following neurofeedback

Mariela Rance [a], Christopher Walsh [a], Denis G. Sukhodolsky [b], Brian Pittman [c], Maolin Qiu [a], Stephen A. Kichuk [c], Suzanne Wasylink [c], William N. Koller [a], Michael Bloch [c], Patricia Gruner [c], Dustin Scheinost [a,b], Christopher Pittenger [b,c,d], Michelle Hampson [a,b,c,*]

[a] Department of Radiology and Biomedical Imaging, Yale University School of Medicine, New Haven, CT 06520, USA
[b] Child Study Center, Yale University School of Medicine, New Haven, CT 06519, USA
[c] Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06511, United States
[d] Department of Psychology, Yale University, New Haven, CT 06520, USA

Randomized, sham-controlled trial of real-time fMRI neurofeedback for tics in adolescents with Tourette Syndrome

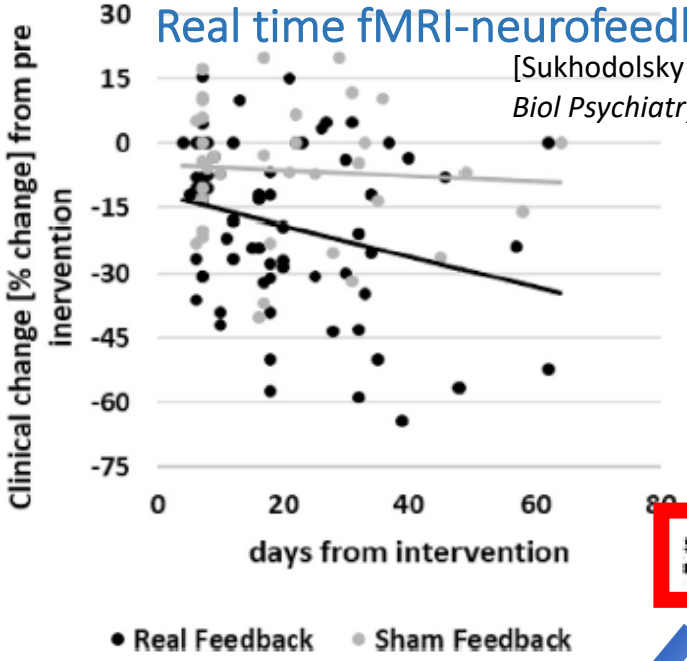
Denis G. Sukhodolsky[1], Christopher Walsh[2], William N. Koller[2], Jeffrey Eilbott[3], Mariela Rance[2], Robert K. Fulbright[2], Zhiying Zhao[2], Michael H. Bloch[1], Robert King[1], James F. Leckman[1], Dustin Scheinost[1,2,4], Brian Pittman[5], Michelle Hampson[1,2,5,*]



- Significant superiority to sham [3.8 point difference on YGTSS-TTS, SMD: 0.59]
- Symptoms keep improving long after the end of the intervention

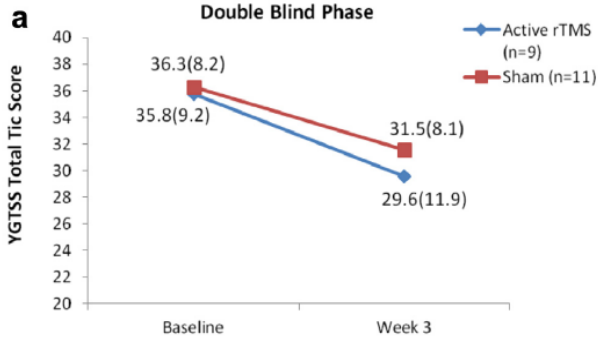
Real time fMRI-neurofeedback

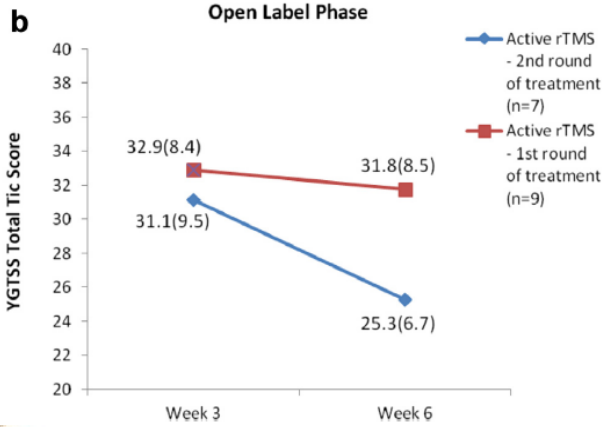
[Sukhodolsky et al., *Biol Psychiatry* 2019]



rTMS

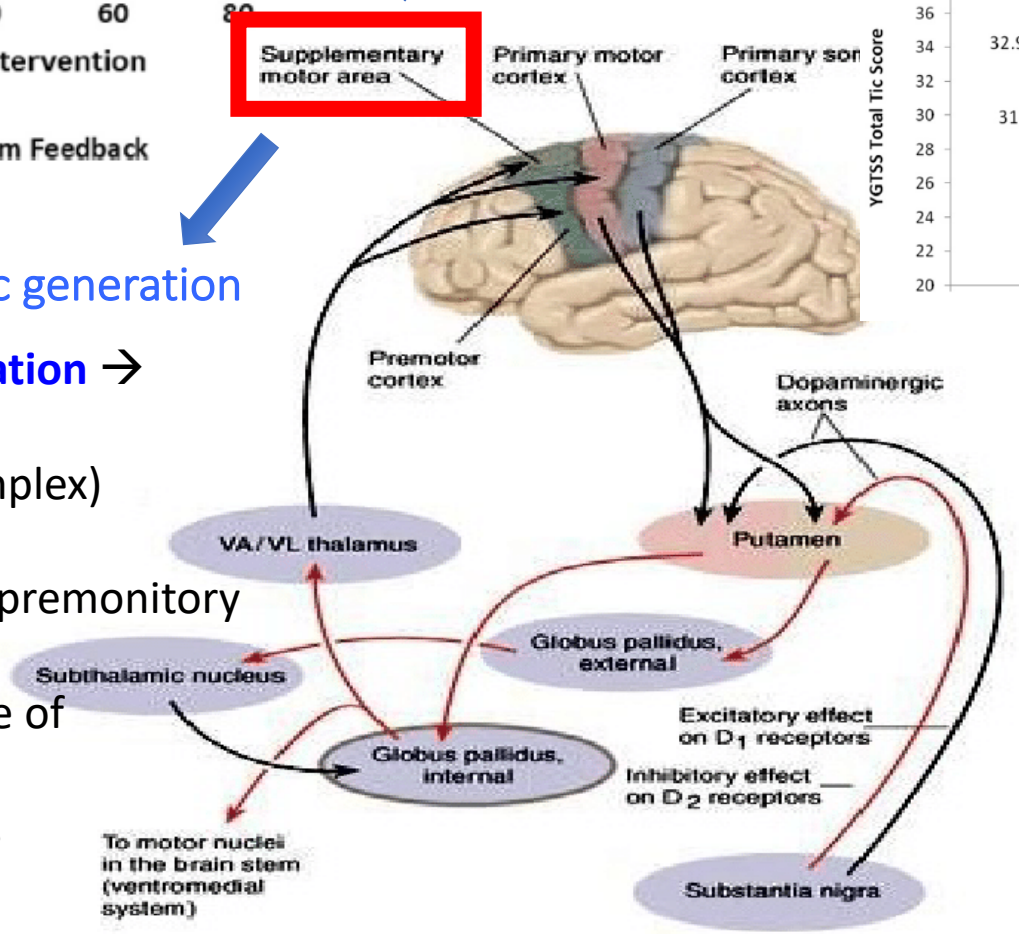
[Landeros-Weinberger et al., *Brain Stim* 2015]





Tic suppression

Tic generation



SMA (proper) excitation → movements
(from simple to complex)
and urges to move
(reminiscent of the premonitory urges of TS),
paralleling the range of phenomena
seen in tic disorders

Never performed in conjunction with behavioral strategies

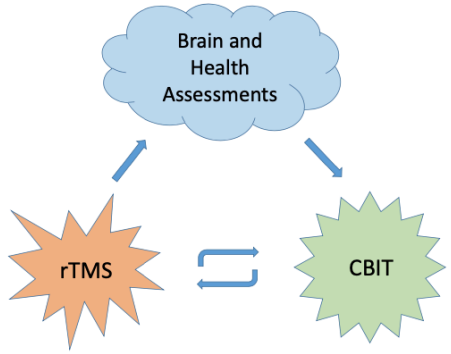
Tourette's Syndrome Research Study

UNIVERSITY OF CALGARY

We are combining new therapies to help treat the tics that occur with Tourette's syndrome and would welcome your help!

Who are we looking for?

1) Children with Tourette's Syndrome
2) Between the ages of 6 and 18 years
3) No more than 4 prior CBIT sessions



Non-invasive = no needles, no contrast, no medicines.
Your child gets to watch lots of movies and play games with us while we work to help them control their tics!

The treatment involves:

1) 8 hours of Comprehensive Behavioral Intervention for Tics (CBIT) therapy
2) 20 hours of repetitive Transcranial Magnetic Stimulation (rTMS) therapy

What is CBIT?

- A combination of behavioral therapy and habit reversal therapy to help manage tics. This therapy teaches people how to recognize the urge to tic, then perform a different action instead of the tic.

What is rTMS?

- A safe and non-invasive brain stimulation therapy that may help calm down an overactive area of the brain in people with Tourette's Syndrome.

Please contact brainkids@ucalgary.ca or call 403-955-2784

Alberta Health Services

This study has been approved by the University of Calgary Conjoint Health Research Ethics Board (REB18-0220)

Alberta Children's HOSPITAL

Courtesy of Dr. Frank MacMaster and Rose Swansburg

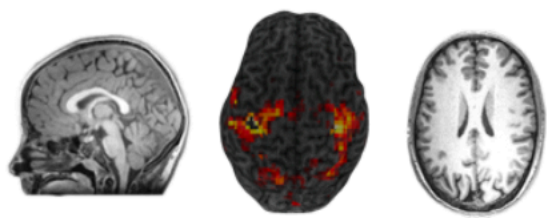
How long does the study take?

- The CBIT therapy is 8 sessions over 10 weeks (Monday's, 60 minutes/session)
- The TMS therapy is 20 sessions over 5 weeks (T-F, 60 minutes/session)
- Mental health assessments, brain imaging scans and brain activity assessments before and after the intervention (approximately 4-8 hours at 3 time points before and after the CBIT+TMS intervention)

What are the benefits to you and your child?

- Our goal is to improve your child's ability to control their tics
    - We expect to see a decrease in tic expression and severity with this intervention
- We will share your child's mental health and tic-related assessment results with you
- We can share pictures of your child's brain from the MRI scan!

Please contact brainkids@ucalgary.ca or call 403-955-2784



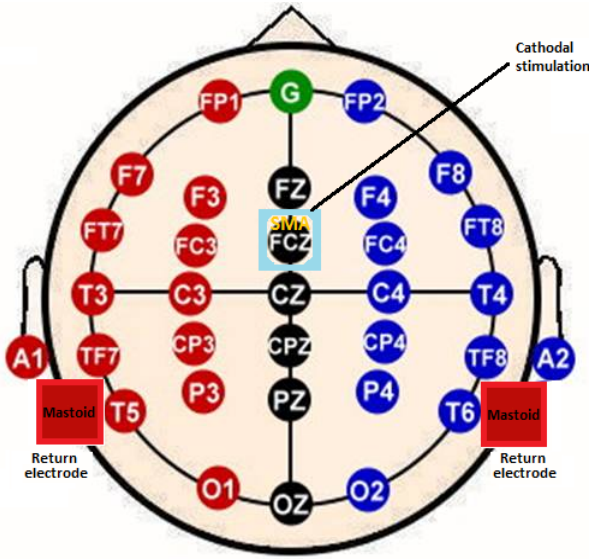
This study has been approved by the University of Calgary Conjoint Health Research Ethics Board (REB18-0220)

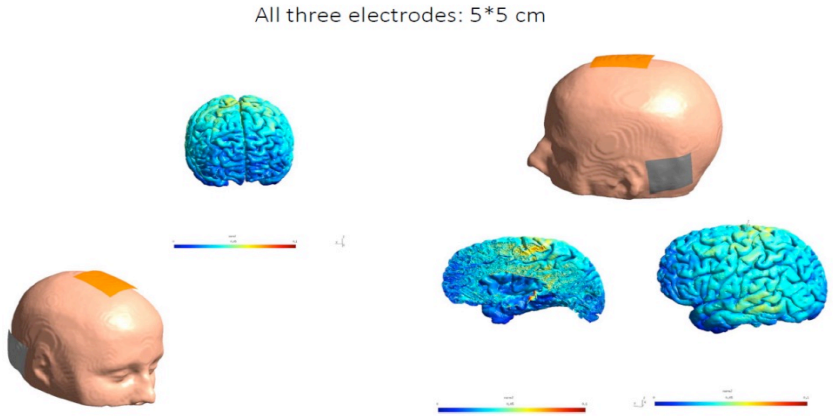
Alberta Children's HOSPITAL

Cathodal bilateral tDCS of SMA [TIC-tDCS]

Safe, non-invasive, inexpensive and exportable

Single session of 1 mA cathodal tDCS over SMA x 20' → acute effect of tic decrease lasting up to 90' in a RCT, sham-controlled (Dyke K…Jackson S, *Exp Brain Res* 2019)

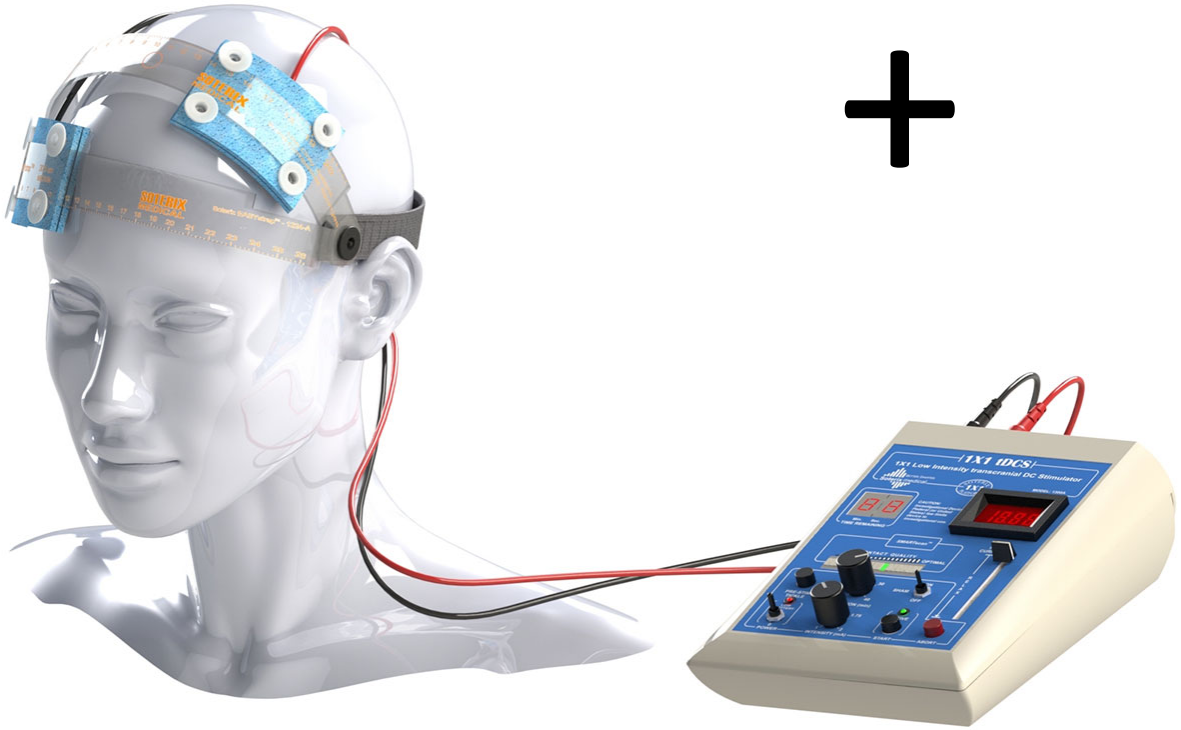




- Effects can increase after repeated stimulation: "**cumulative dosing**" (Alonzo et al., *Brain Stim* 2012)

- Principle of **activity-selectivity**: functional specificity where an active neuronal network is more likely to be modulated by tDCS than an inactive one → 1mA cathodal SMA tDCS reduced impulsive behavioral responses more efficiently while performing a stimulus-response compatibility task (Spieser et al., *J Neurosci* 2015)

Cathodal bilateral tDCS of SMA [TIC-tDCS] + behavioral strategy (acc. to Habit reversal training principles)



+

Competing motor response training (6-8 weeks) and implementation during stimulation

Cathodal bilateral tDCS of SMA [TIC-tDCS]

NCT: 03401996

Screening for eligibility

Randomization

Informed consent procedure

Active tDCS n=12

n=5
3 M
Median age 22
[17-55]

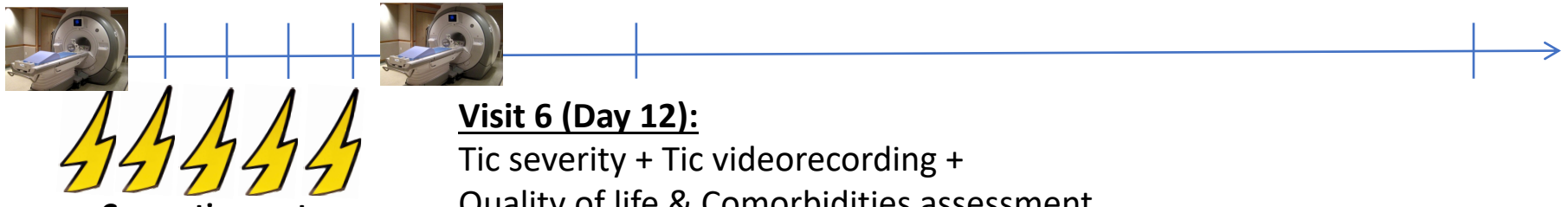
Diagnosis of TS
Age >16 years
Stable psychotropic treatment

N=7
5 M
Median age 28
[21-61]

Sham n=12

- **Primary outcome**: Yale Global Tic Severity Scale, total tic severity sub-score (0-50)
- **Secondary outcomes**: Premonitory Urges for Tics (PUTS) scale, Inhibition potency based on video-based tic count [('Free-to-tic' score – 'Suppressing tics' score)/ 'Free-to-tic' score]
- Quality of life & Comorbidities assessment – Patient expectation and tolerability
- Pre- and Post-treatment **rs-fMRI scan** (if feasible)

Visit 7 (Day 39):
Tic severity assessment



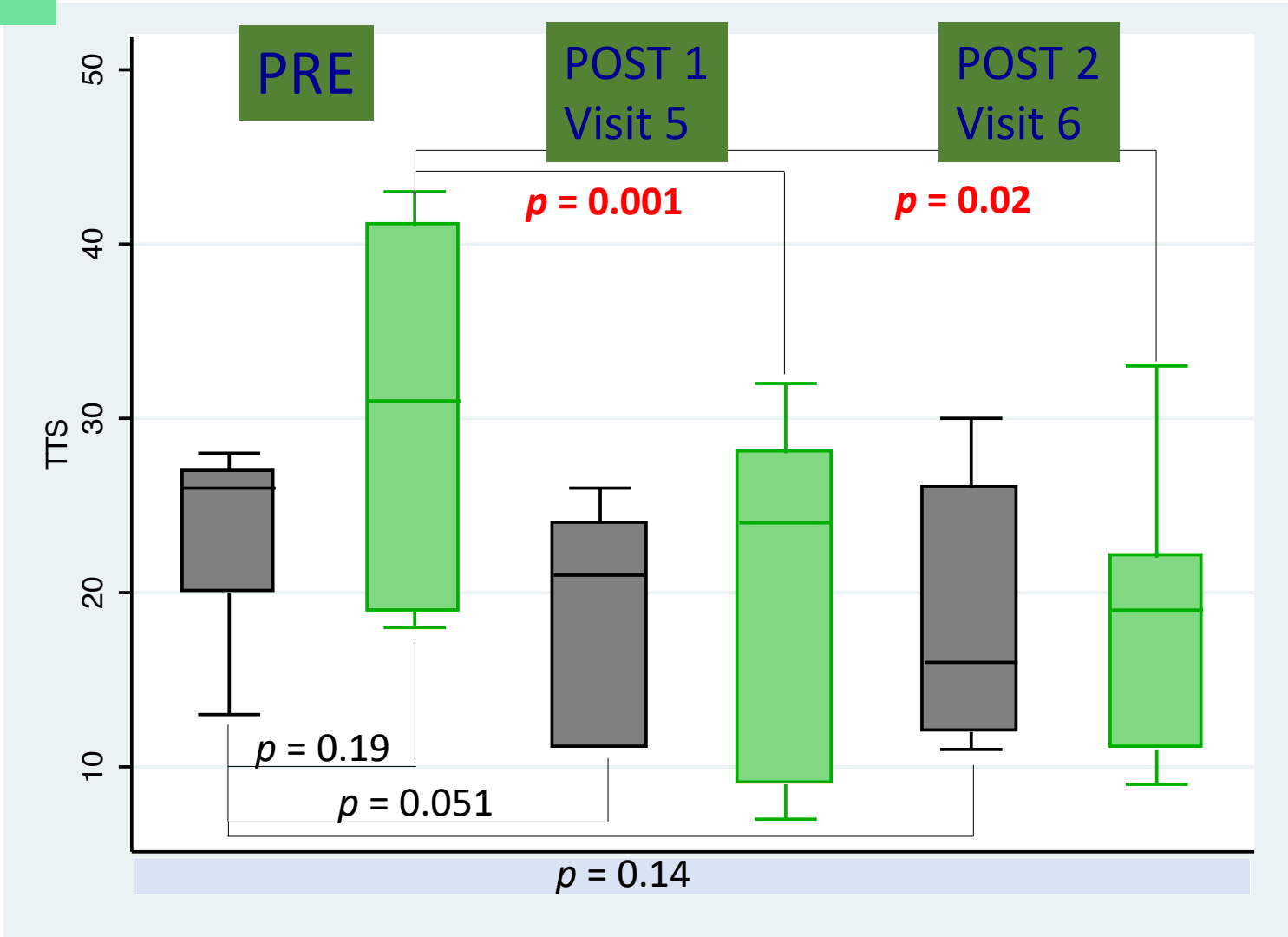
Competing motor response

Visit 6 (Day 12):
Tic severity + Tic videorecording +
Quality of life & Comorbidities assessment

SHAM

REAL

YGTSS total tic severity score (interim n = 12: 5 real, 7 sham)



Preliminary considerations

- tDCS over bilateral SMA appears to be very well tolerated, at least when administered over 5 consecutive days (transient headache in one participant in each group)
- Initial promising signal of efficacy in decreasing tic severity (and possibily premonitory sensations/urges), but disjoint from tic suppressing capacity
- Analyses to come will involve rs-fMRI data and relationship between patient expectation and responsiveness, as well as comorbidity profile and responsiveness
- If positive, this trial should be followed by a larger trial, comparing different treatment durations and home-based vs. hospital-based administration

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N3 Non-invasive Neurostimulation Network

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