

# **Focal Brain Stimulation for PTSD**

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# Disclosures

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**Grant / Research Support:** NARSAD; NIH; VA

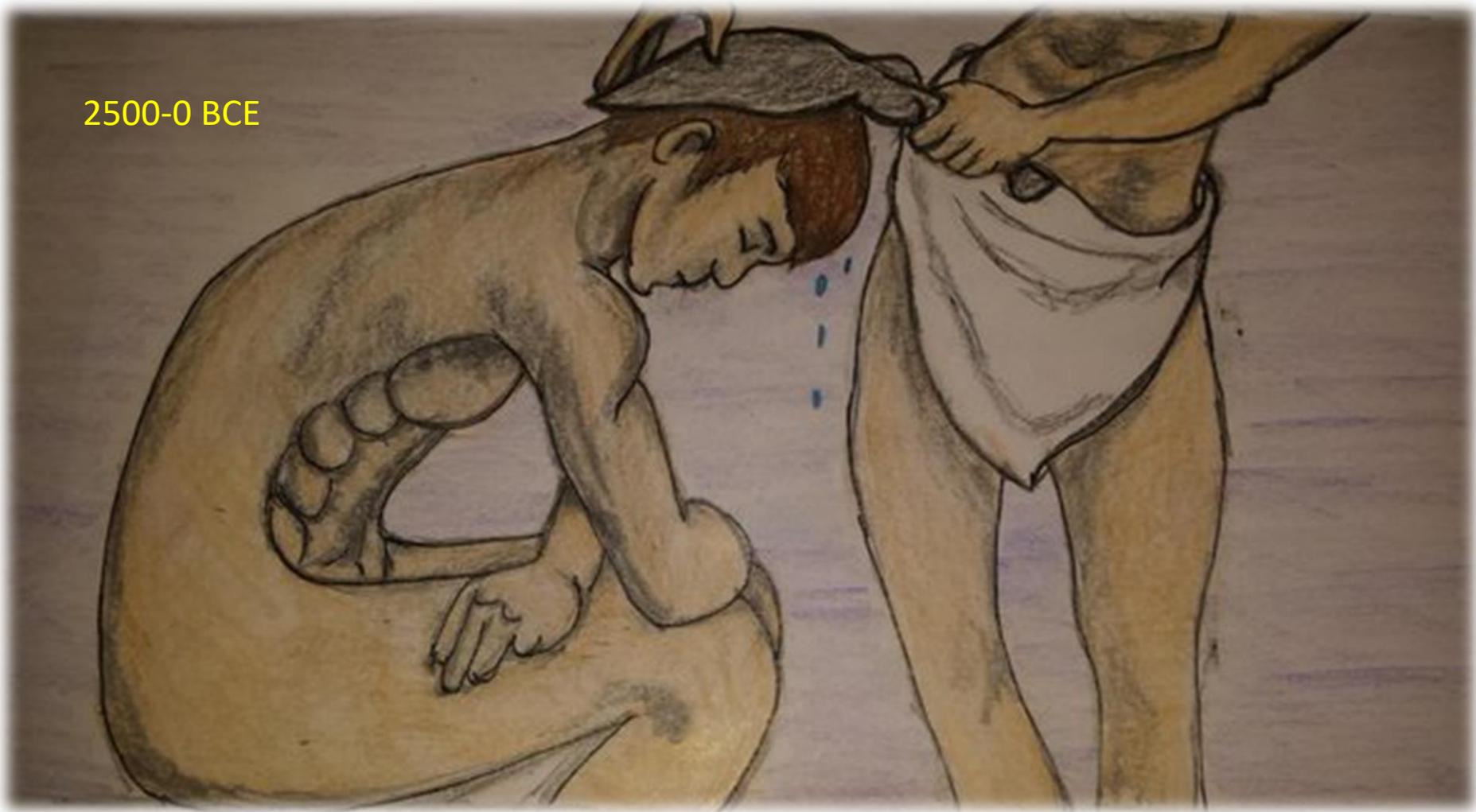
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**Stock Shareholder/IP:** None

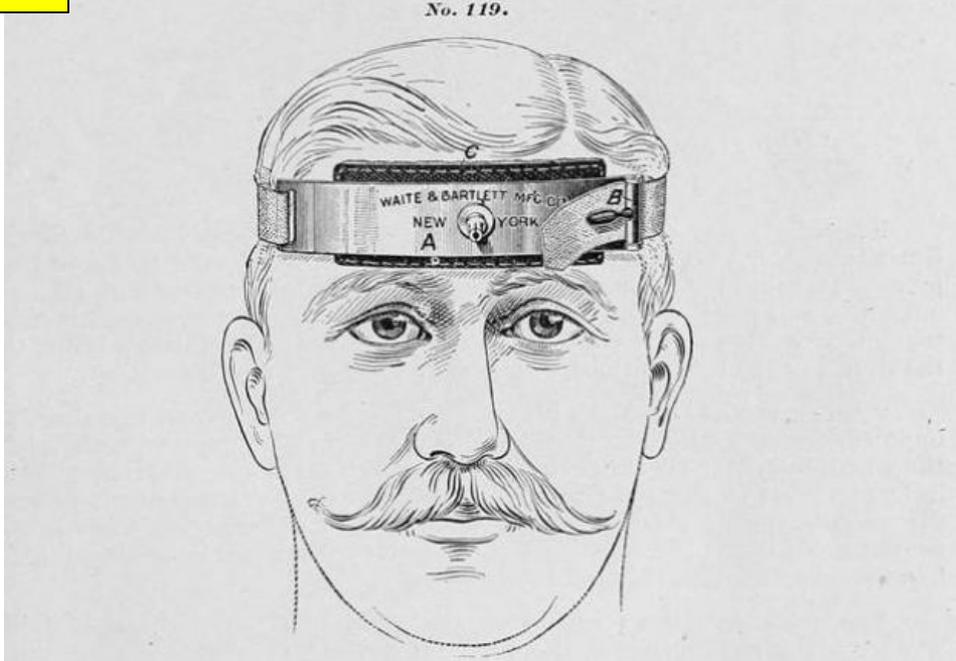
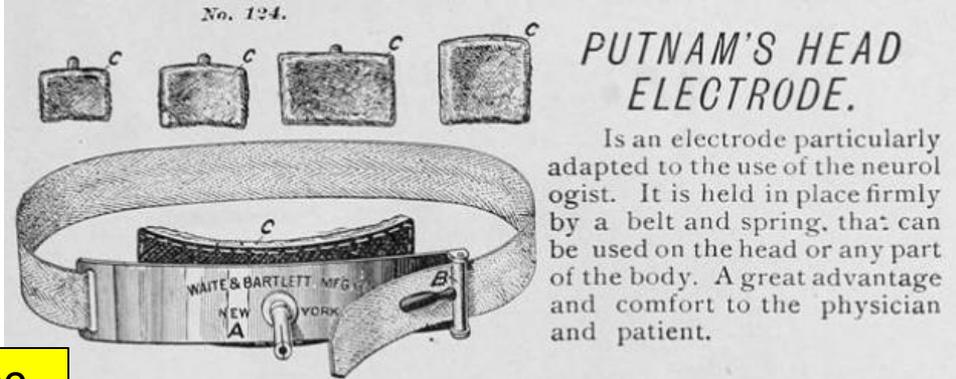
This presentation describes the experimental use of devices and medications that have only been approved by the U.S. Food and Drug Administration except for research purposes

2500-0 BCE

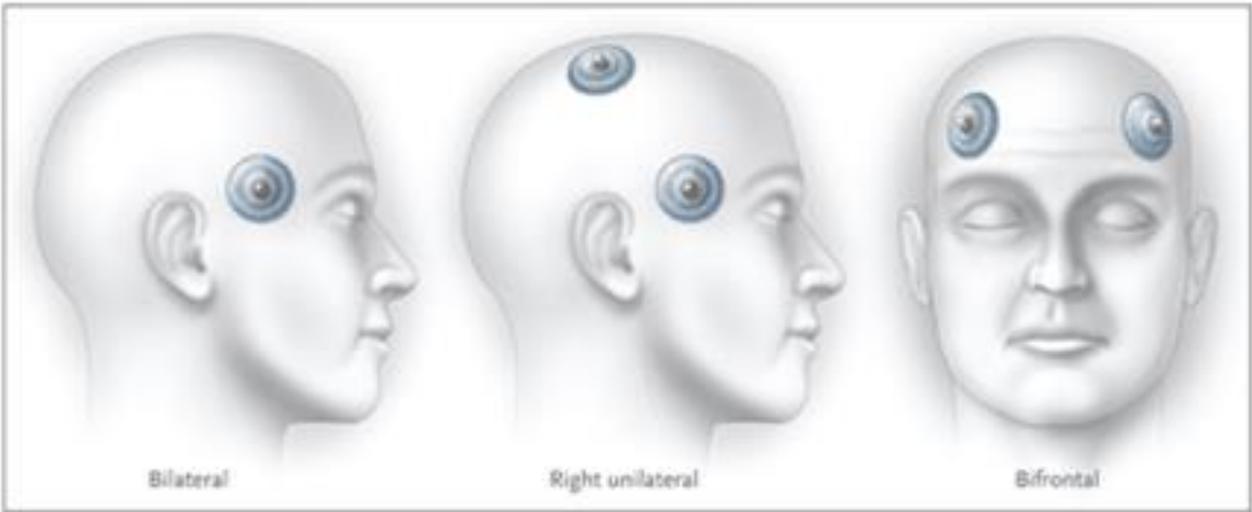
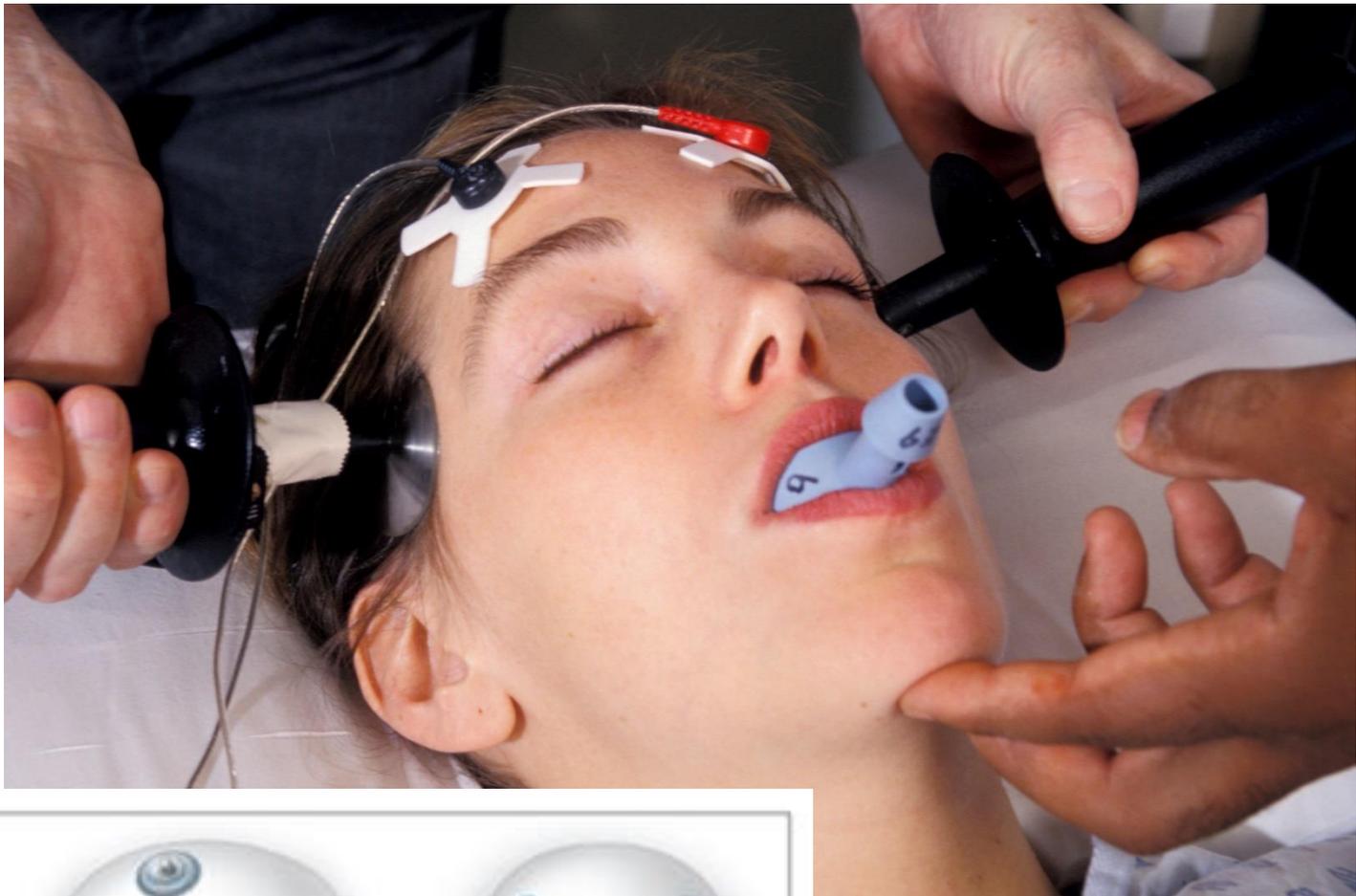




1700s-1900s



**ECT**





Dr. Margaret Patterson with an early cranial electrotherapy system

*'The Black Box' (MECANET Model IV) as shown on the BBC film, with Meg demonstrating the controls. 1980*



*Meg with Pete Townshend, after his treatment. 1982*

1960s-1980s

# Treatment paradigms

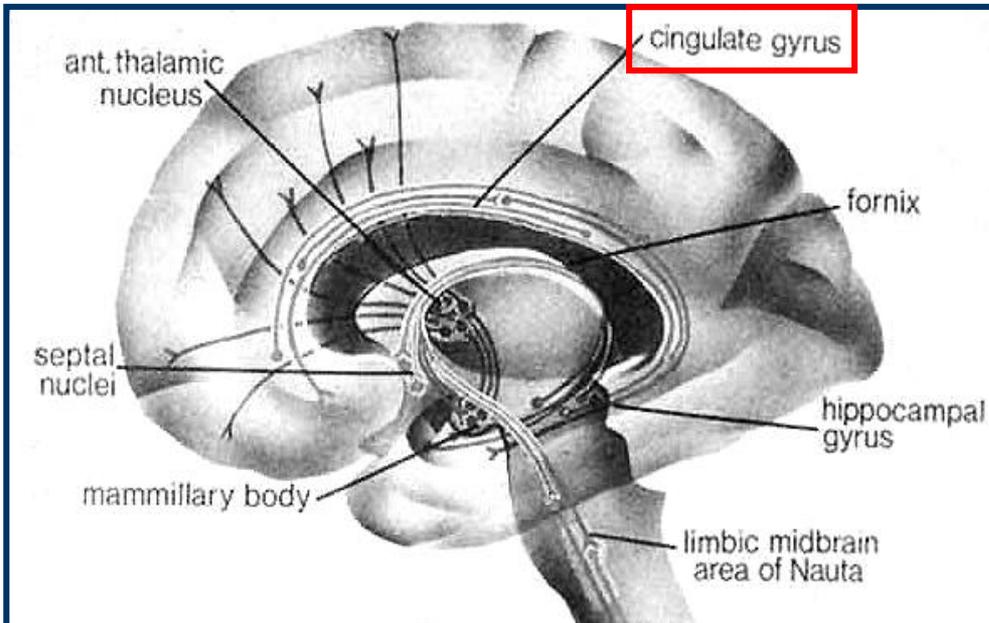
- Behavioral/psychological
- Chemical/neurochemical
- Neuroanatomical/neural circuit

# Neural Circuit Paradigm for Tx

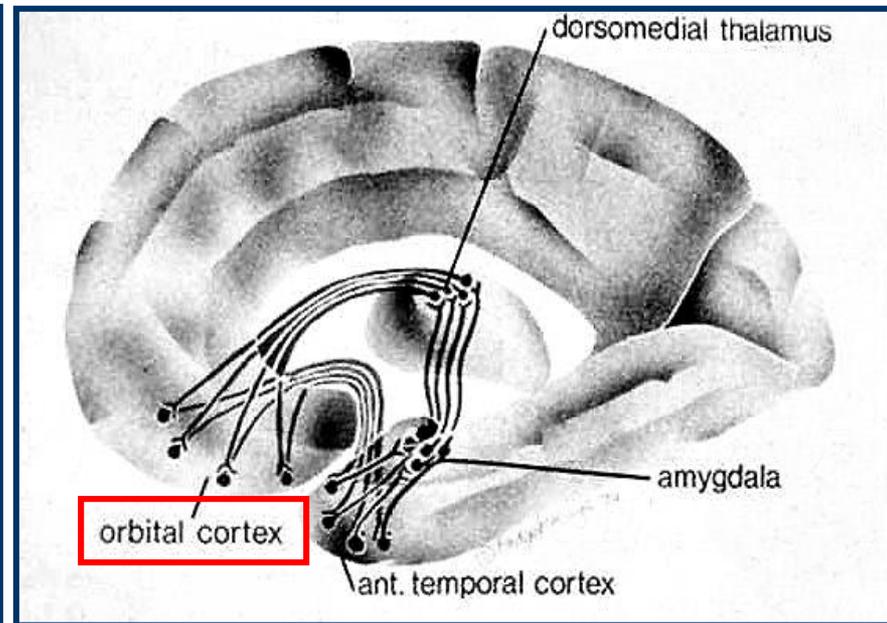
- Delineate the neural circuitry of the disorder of interest (or relevant symptom domains)
- Identify key nodes
- How could focal brain stimulation affect the node and connected network?

# Mood/Thought/Behavior Circuits

Papez, 1937

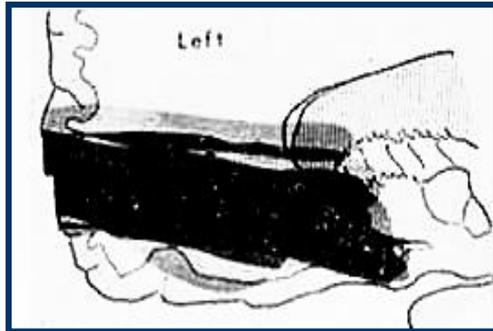


**Medial  
Limbic Circuit**

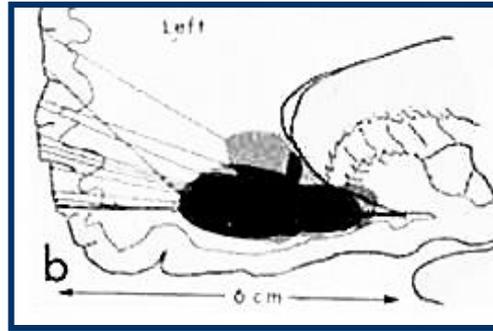


**Basolateral  
Limbic Circuit**

# Surgical Approaches: White Matter Disconnection



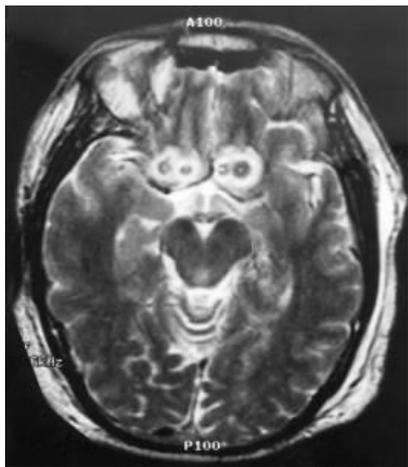
Orbital undercutting



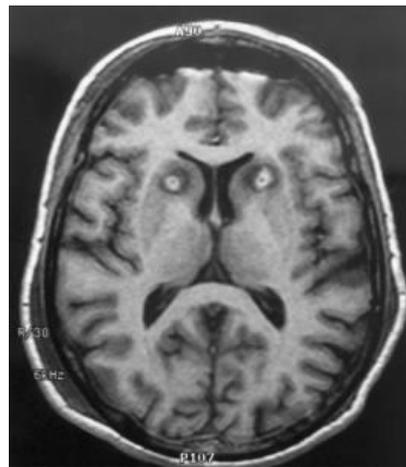
Ytrium subcaudate tractotomy



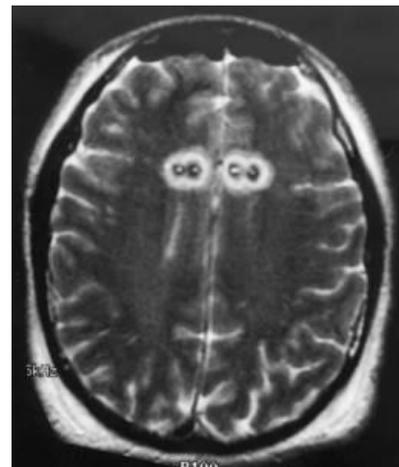
Cingulo-tractotomy



Subcaudate Tractotomy



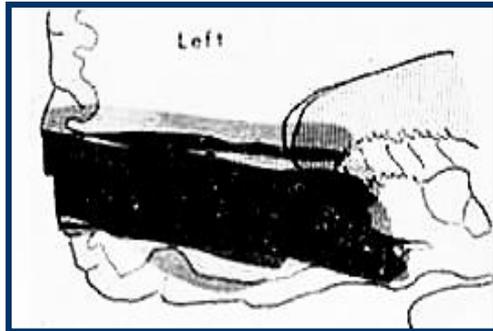
Anterior Capsulotomy



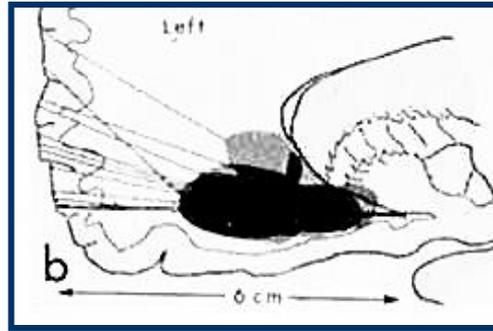
Anterior Cingulotomy

- **22-75% efficacy**
  - No controlled studies
  - Not disorder specific
- **Adverse effects:** seizures, pers  $\Delta$ , cognitive abnorm.

# Surgical Approaches: White Matter Disconnection



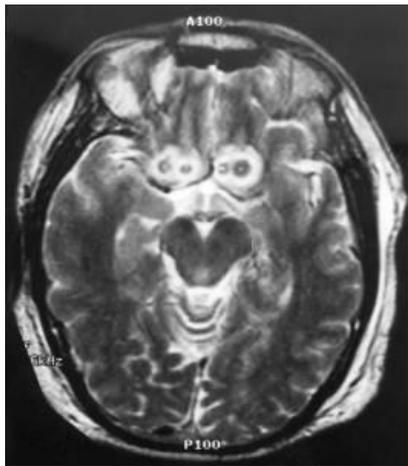
Orbital undercutting



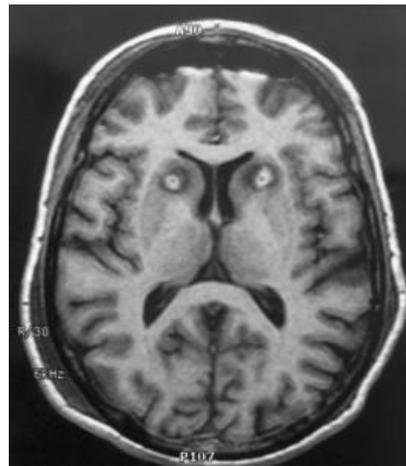
Ytrium subcaudate tractotomy



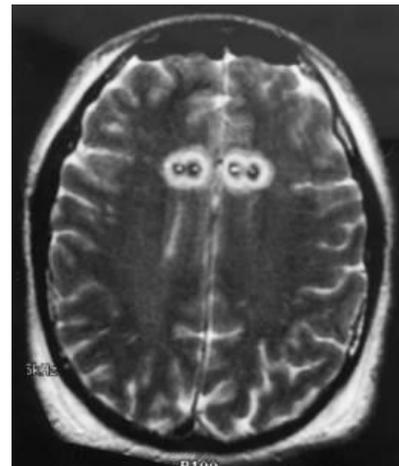
Cingulo-tractotomy



Subcaudate Tractotomy



Anterior Capsulotomy

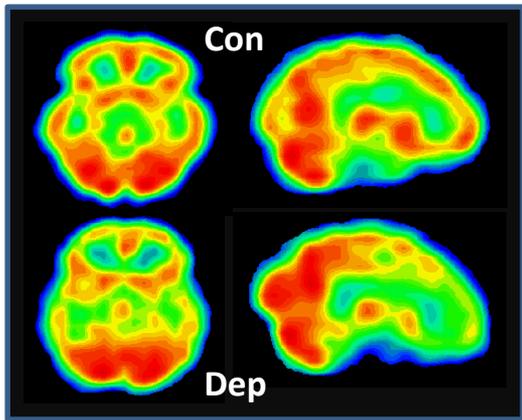


Anterior Cingulotomy

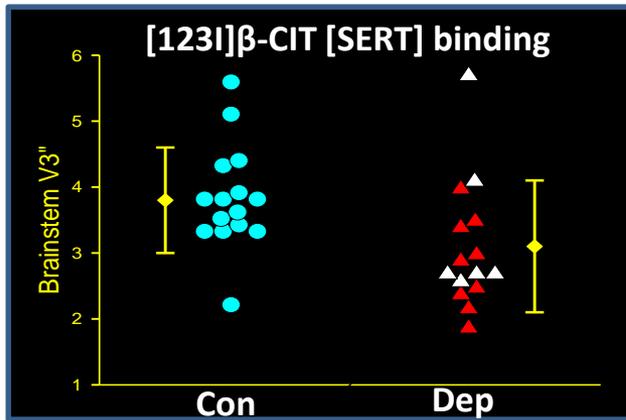
**CHALLENGES:**

**NEED BETTER MODELS**

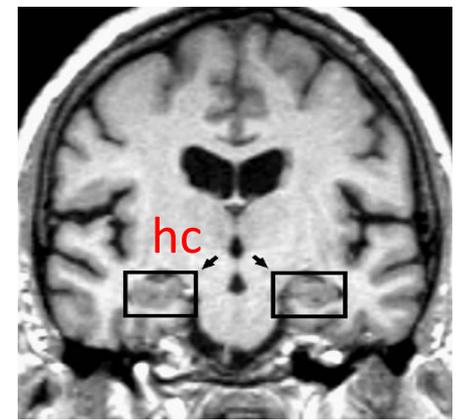
**NEED BETTER METHODS**



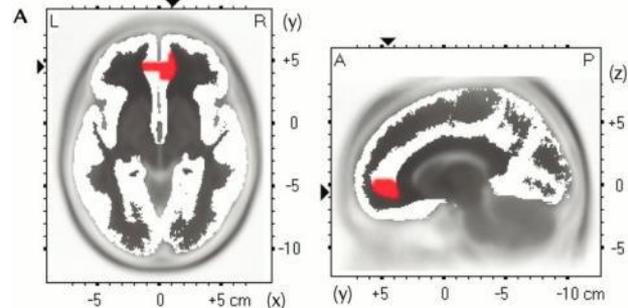
PET/SPECT



Ligand imaging (PET/SPECT)

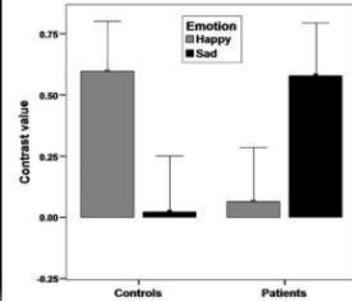
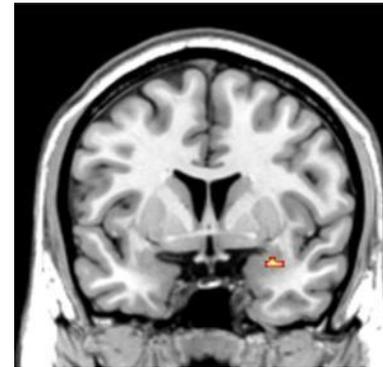


Structural MRI

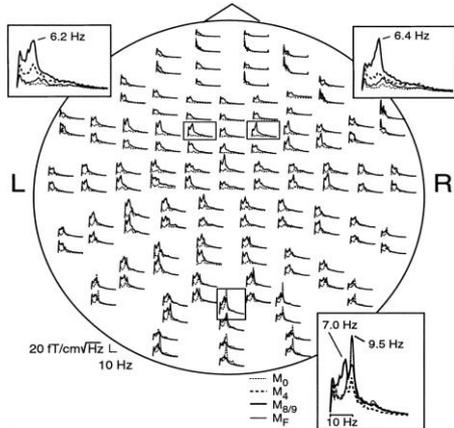


EEG

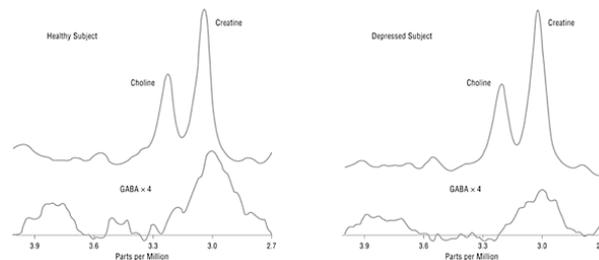
**Neuroimaging methods**



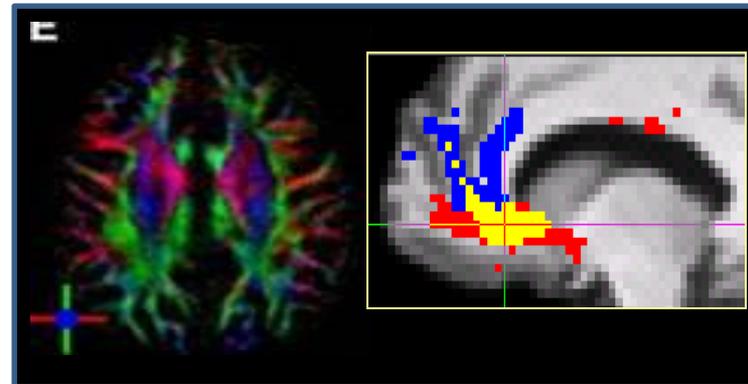
Functional MRI



MEG

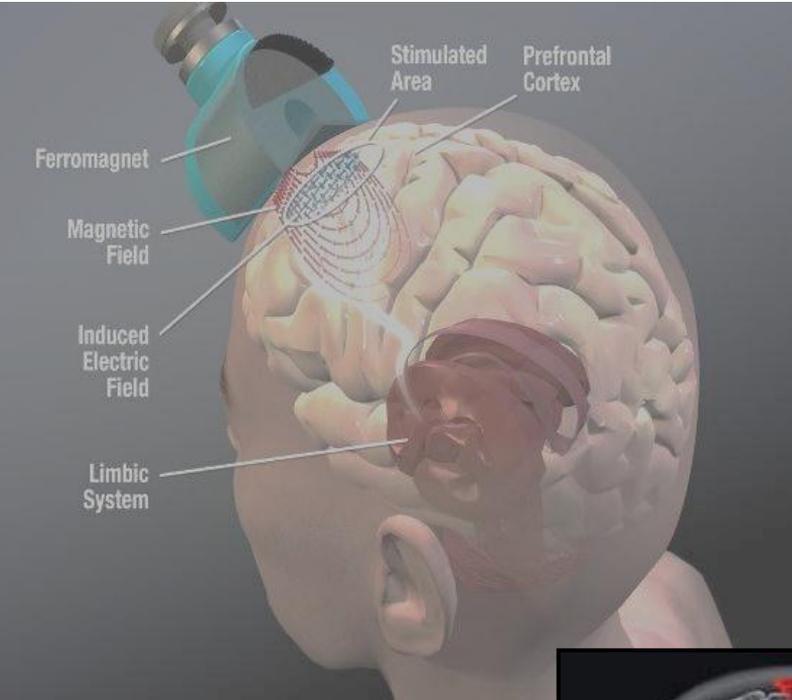
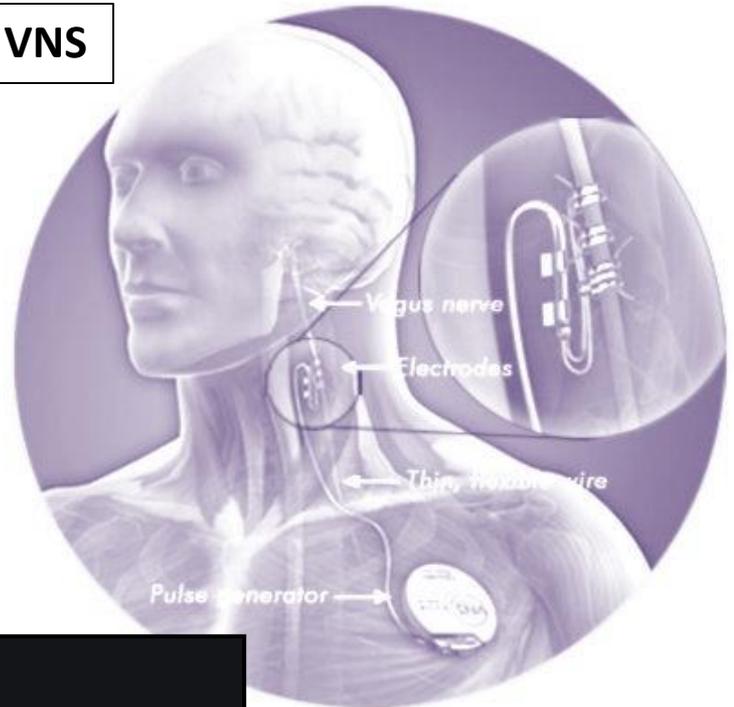


MRS

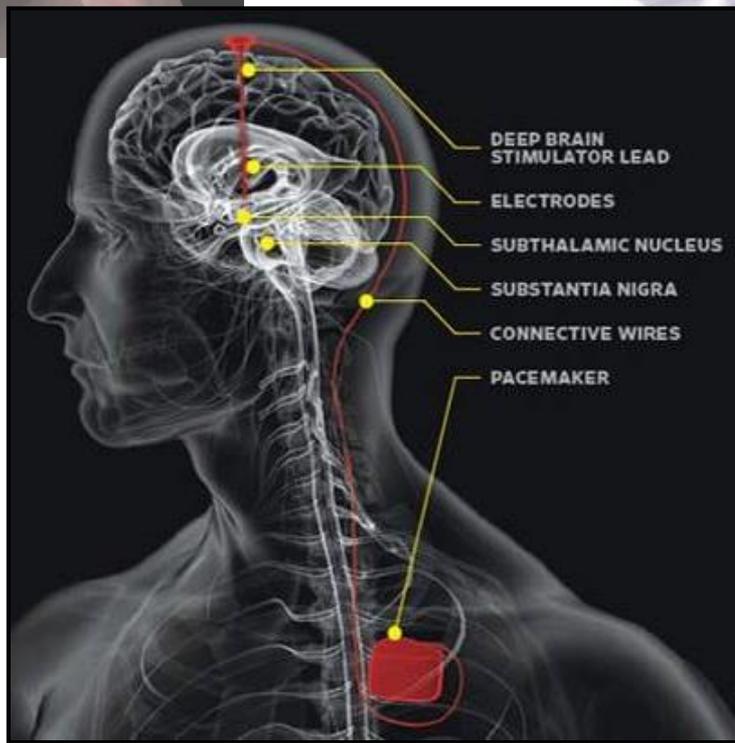


DTI

VNS

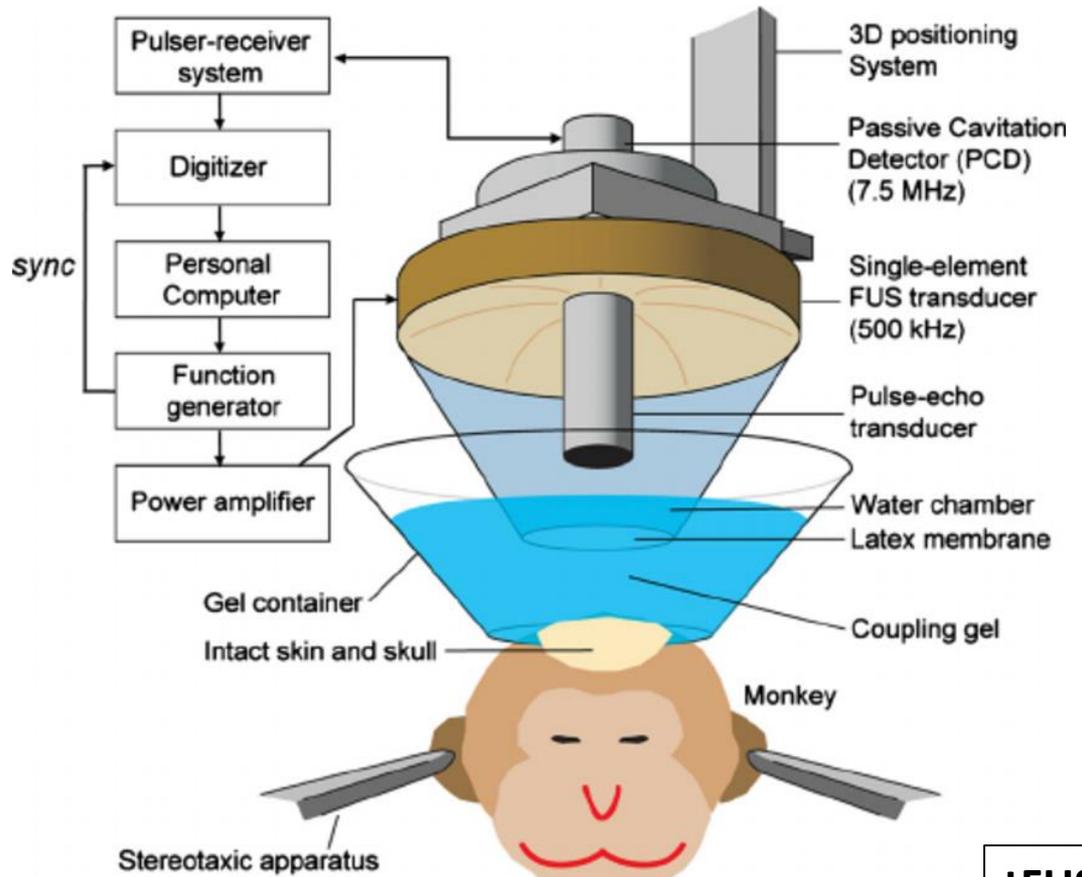
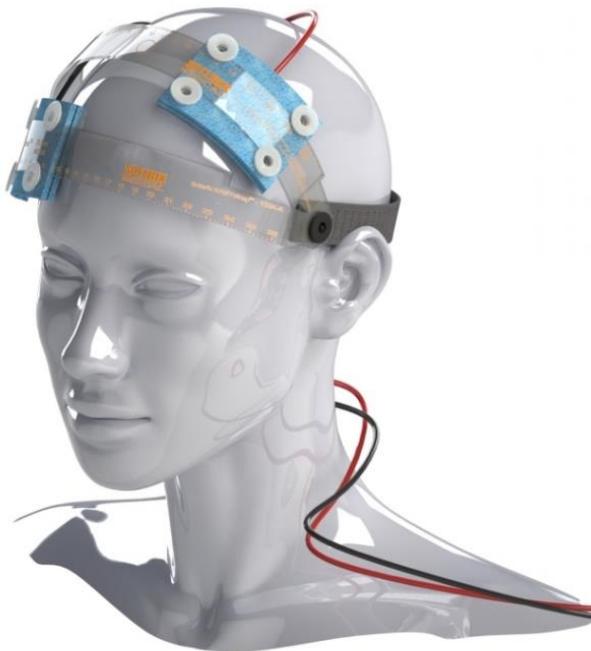


TMS

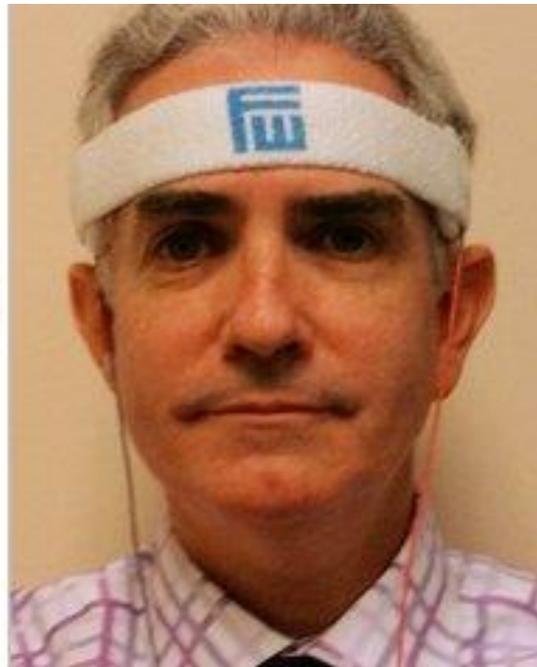
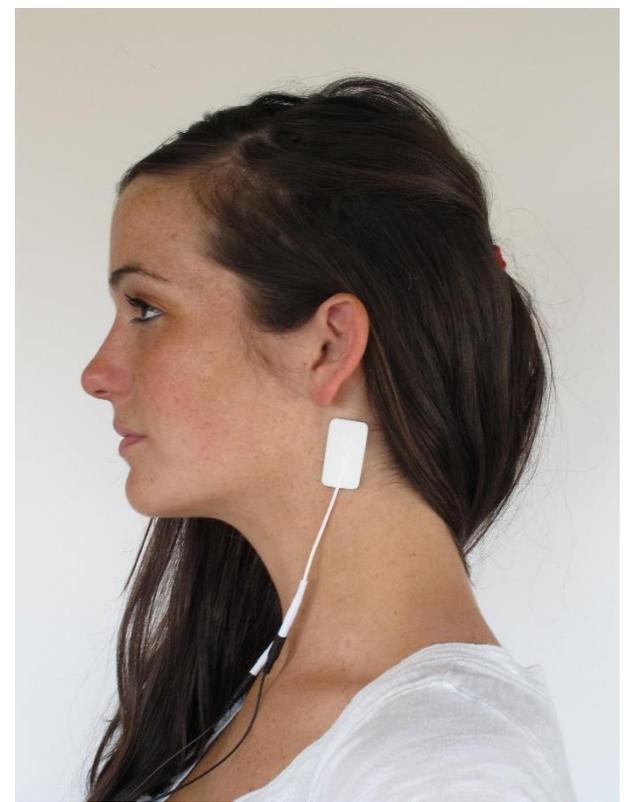


DBS

tDCS

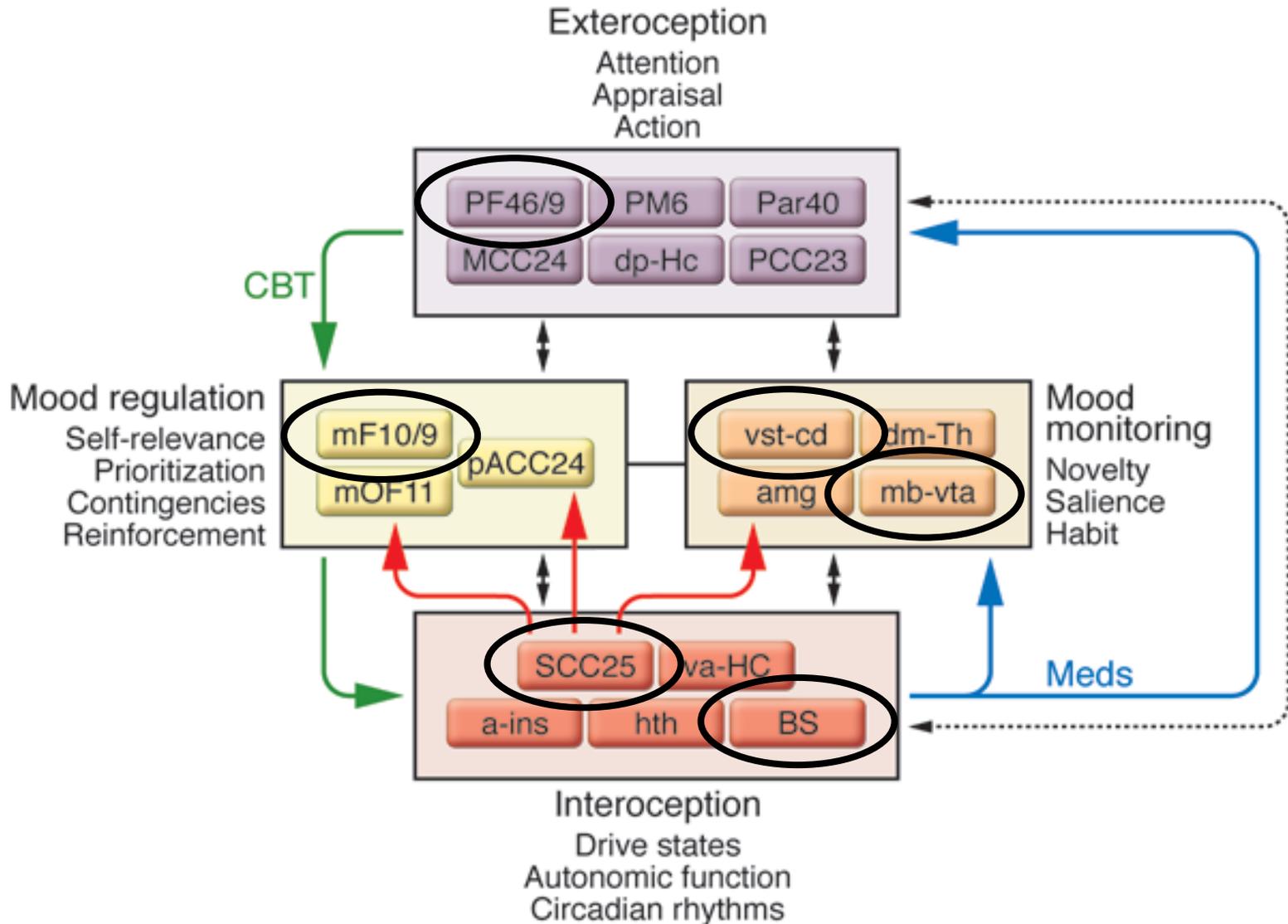


tFUS



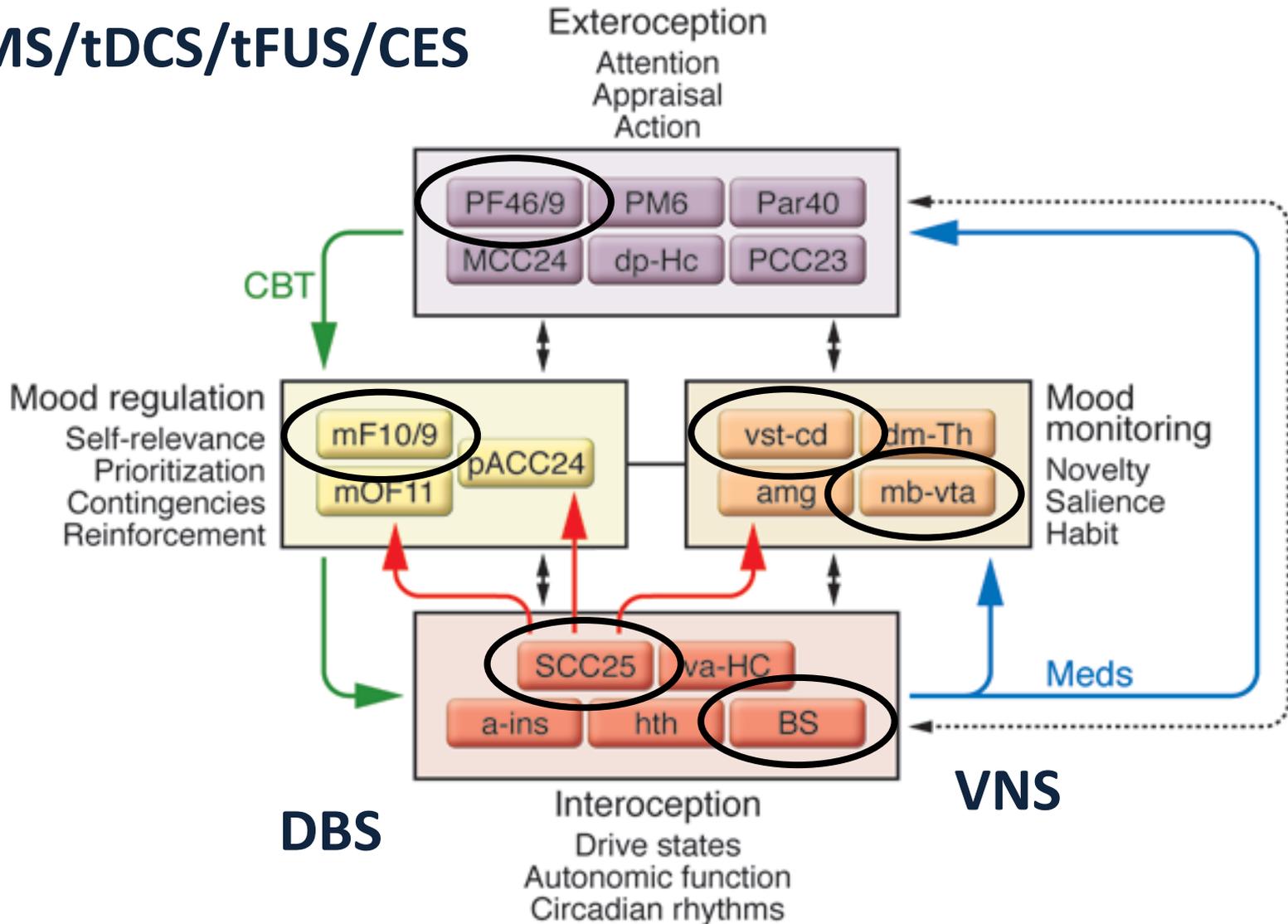
**CES (tACS)**

# Putative “Depression” Network

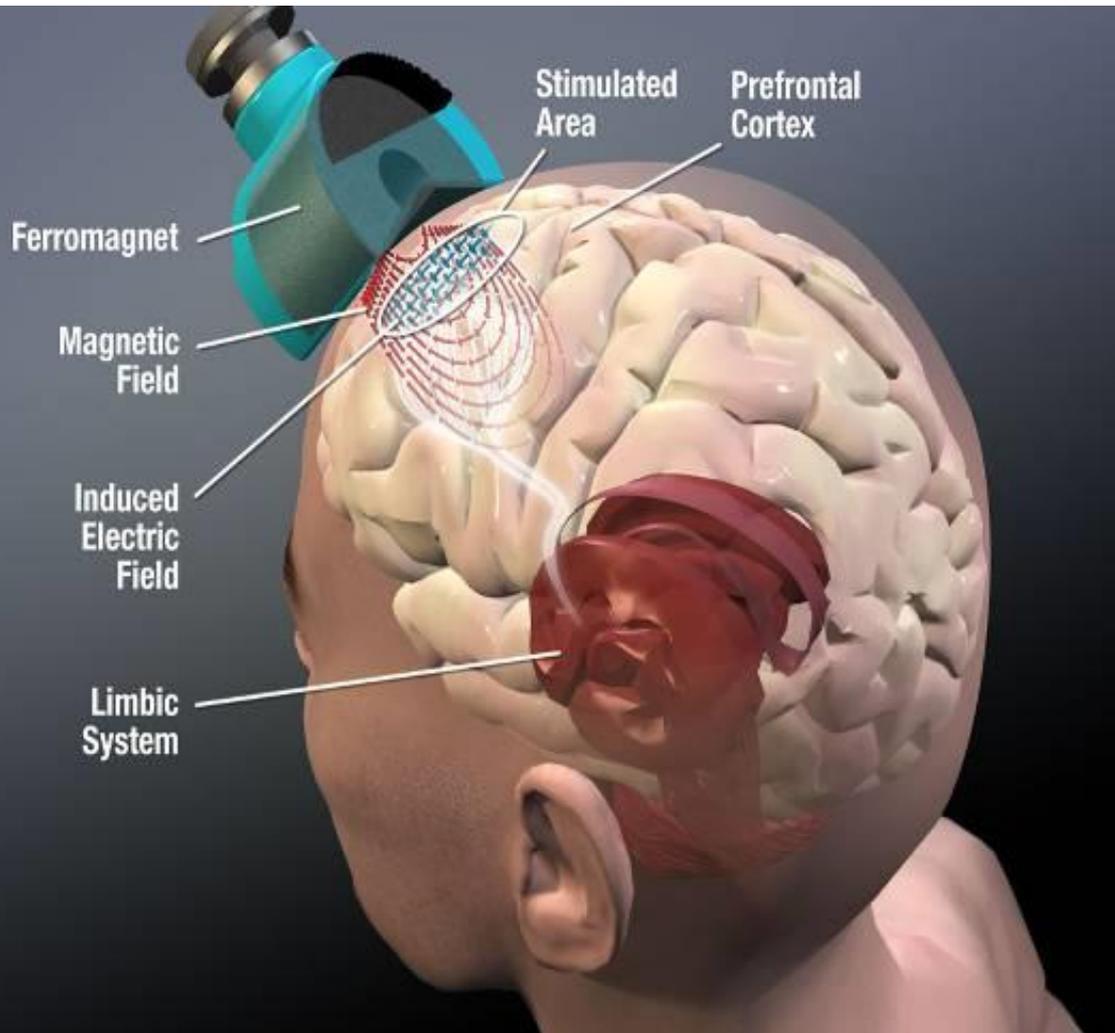


# Putative “Depression” Network

**TMS/tDCS/tFUS/CES**



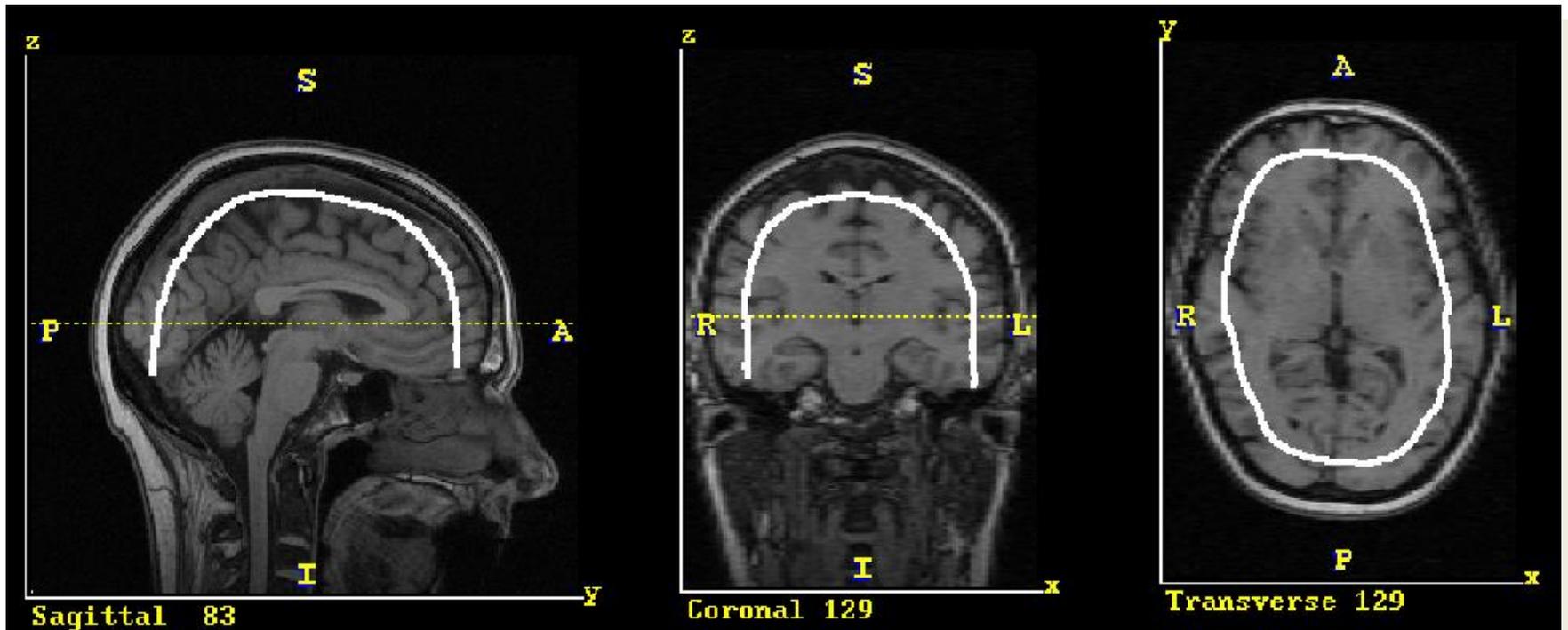
# Transcranial Magnetic Stimulation (TMS)



- **Uses rapidly changing magnetic field to induce current in cortex**
- **Depolarizes cortical neurons focally**
- **Distant effects in connected regions throughout the network**
- **Non-invasive, no anesthesia, patient awake during stimulation**

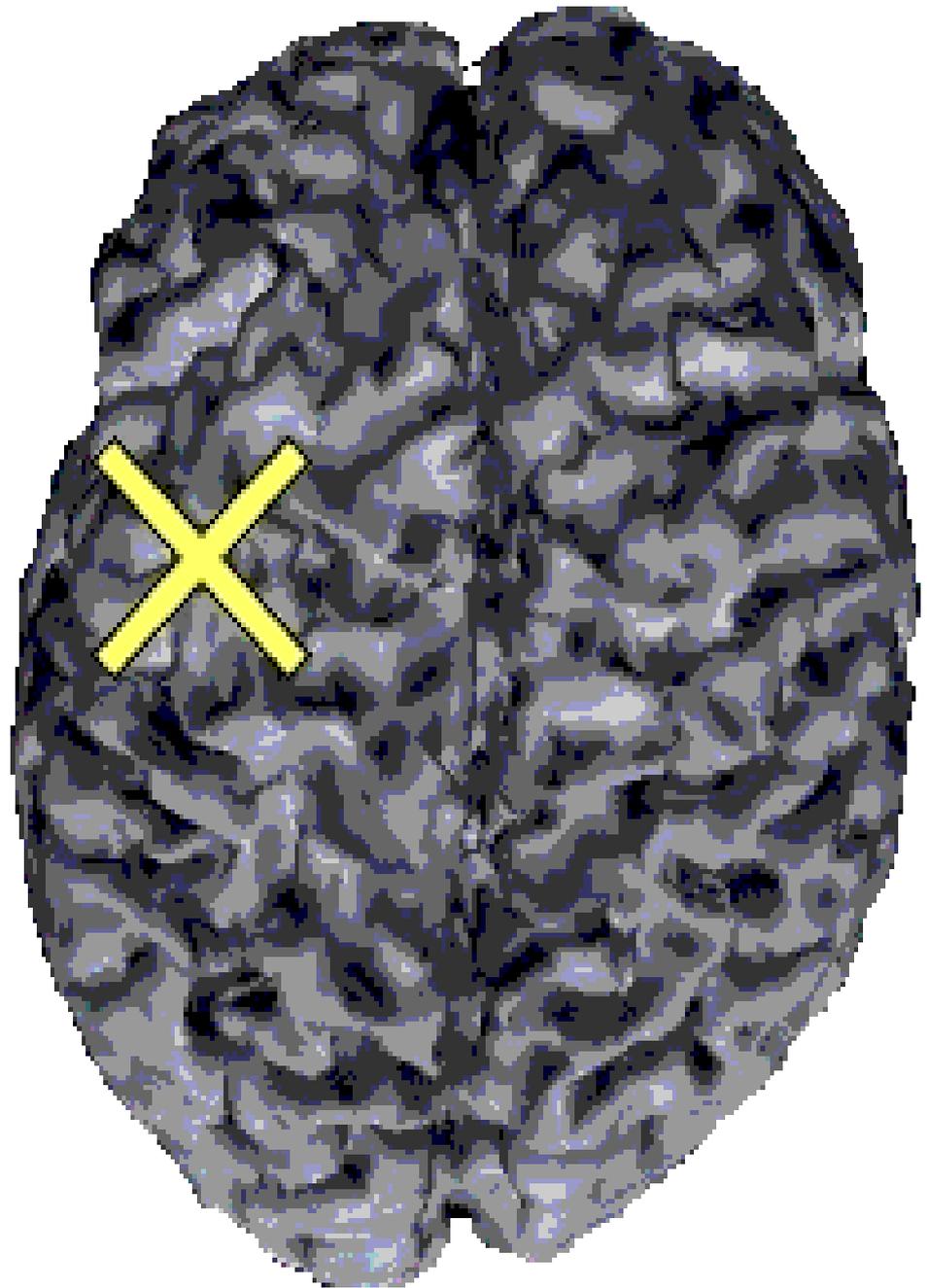
# TMS: Depth of Stimulation

Relative depth reached by current TMS coils



Stimulation at one cortical site leads to rapid changes in activity in other brain areas

Quantitative EEG data over 30 msec



# Repetitive TMS (rTMS)



- **Frequency:** rate of rTMS pulses
  - Slow/low Hz:  $\leq 1$  Hz
  - Fast/high Hz:  $\geq 5$  Hz
- **Intensity:** strength of current induced in cortex
  - Defined as percent (%) of motor threshold (MT)
  - MT defined as intensity inducing motor evoked potential during stimulation of primary motor cortex
- **Train:** series of rTMS pulses
  - **Train duration**
  - **Intertrain interval**

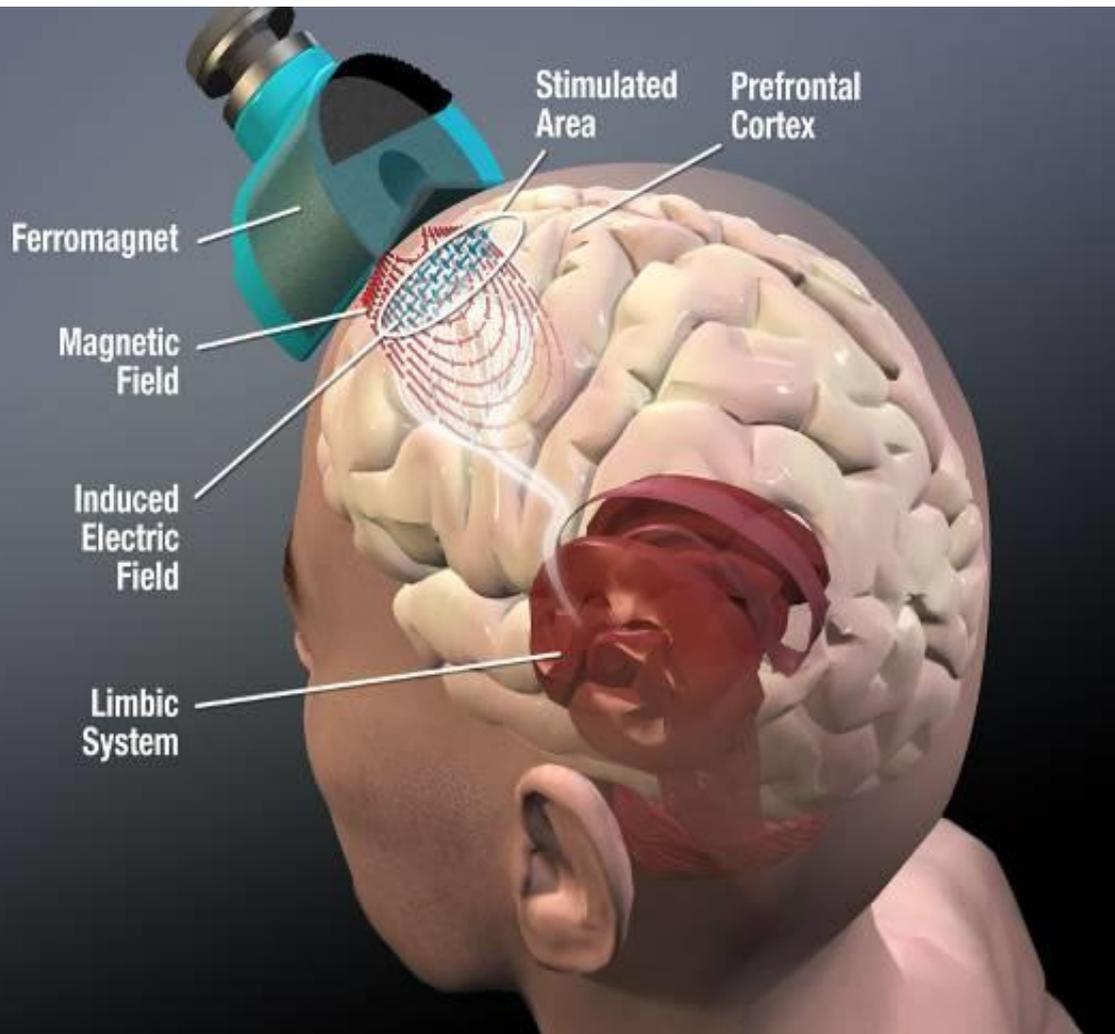
# Side effects and contraindications

- Side effects:
  - Headaches (mild)
  - Pain during stimulation (mild)
  - Seizures (extremely rare with current settings)
  - No cognitive impairments; some patients may show cognitive improvements
- Contraindications:
  - Metal in body, especially head

# Mechanism

- Local and remote changes in brain activity
  - Changes in neural plasticity
  - Modulates oscillatory nature of neural networks (as measured by EEG, diagnostic potential)
  - Altered balance of cortical/subcortical neural systems (e.g., increased in emotional regulation)
- TMS modulates levels of monoaminergic neurotransmitters

# TMS for Depression



- **Location:**
  - Left vs. right dorsolateral prefrontal cortex
- **Parameters:**
  - Left: 5-20 Hz; right: 1 Hz
  - 80%-120% motor threshold
  - ~30-40 min tx
  - 15-30 txs, daily, over 3-6 weeks

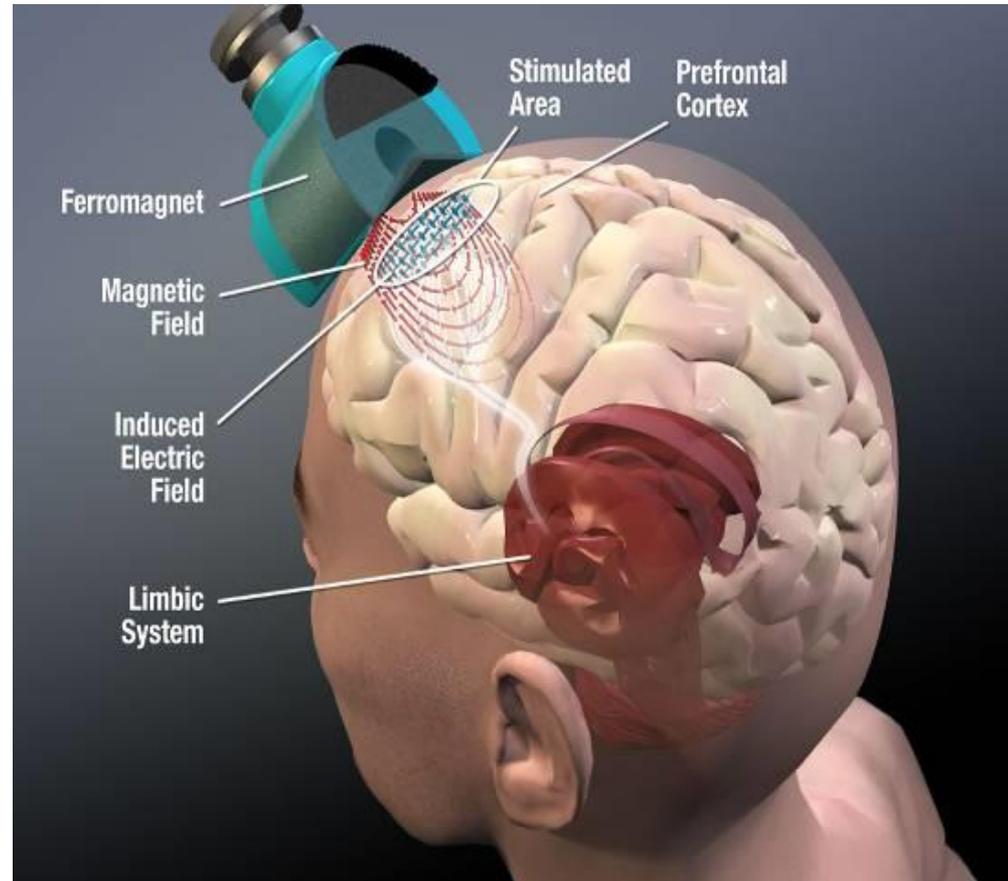
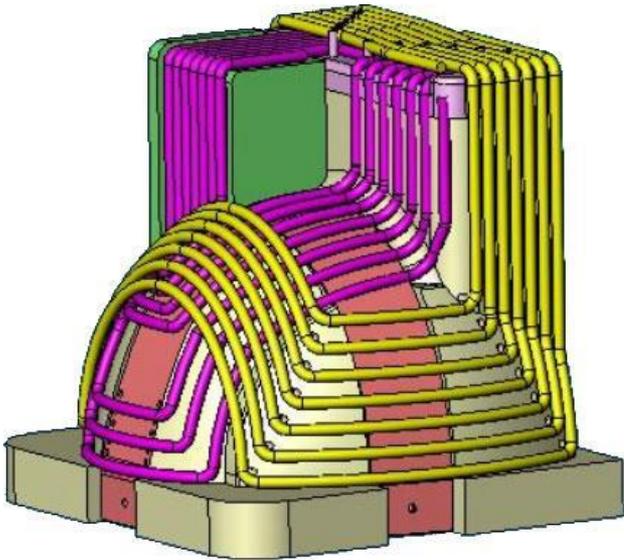
# rTMS: Antidepressant Efficacy

- Studied for depression since 1993
- Multiple meta-analyses confirm statistically significant antidepressant effects
  - Response rates ~20%-40%; up to 60% open-label
- Two large, multi-center trials (combined N=~500) demonstrate antidepressant effects of left dorsolateral prefrontal 10 Hz rTMS

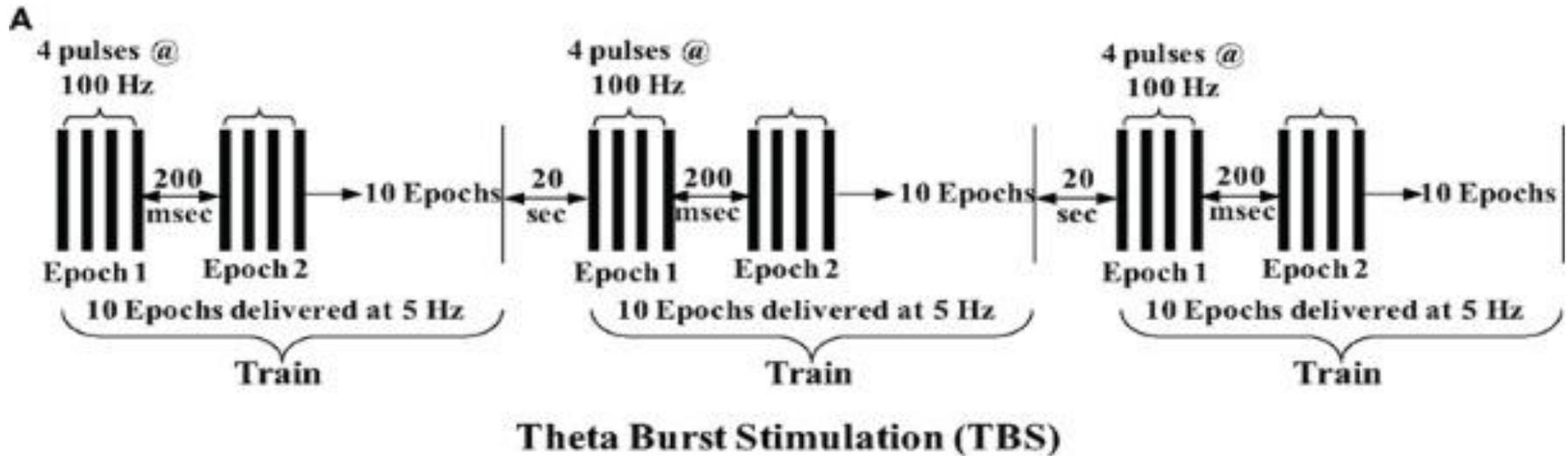
- At least four FDA-approved TMS devices
- Available for tx of depression within VA (TMS Pilot Program)



# “Deep” TMS



# Theta Burst TMS (TBS)



Session length: ~10 min instead of ~40 min

May have unique physiological properties

# Synchronized TMS



- Low intensity TMS
- Delivered at individual's prefrontal alpha frequency (EEG-based)
- Preliminary data suggest potential efficacy for depression
- Practically no seizure risk

# Brain Circuitry Involvement in PTSD

## SENSORIMOTOR CORTEX

*Function:* Coordination of sensory and motor functions

*In PTSD:* Symptom provocation results in increased activation

## THALAMUS

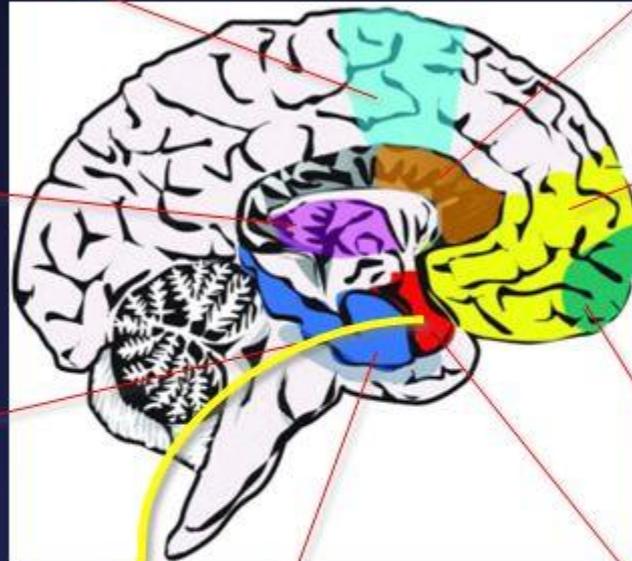
*Function:* Sensory relay station

*In PTSD:* Decreased cerebral blood flow

## PARAHIPPOCAMPAL GYRUS

*Function:* Important for memory encoding and retrieval

*In PTSD:* Show stronger connectivity with medial prefrontal cortex; decreases in volume



## ANTERIOR CINGULATE CORTEX

*Function:* Autonomic functions, cognition  
*In PTSD:* Reduced volume, higher resting metabolic activity

## PREFRONTAL CORTEX

*Function:*

- Emotional regulation

*In PTSD:*

- Decreased gray and white matter density
- Decreased responsiveness to trauma and emotional stimuli

## ORBITOFRONTAL CORTEX

*Function:* Executive function

*In PTSD:* Decreases in volume

## FEAR RESPONSE

*Function:*

- Evolutionary survival

*In PTSD:*

- Stress sensitivity
- Generalization of fear response
- Impaired extinction

## HIPPOCAMPUS

*Function:*

- Conditioned fear
- Associative learning

*In PTSD:*

- Increased responsiveness to traumatic and emotional stimuli

## AMYGDALA

*Function:*

- Conditioned fear
- Associative learning

*In PTSD:*

- Increased responsiveness to traumatic and emotional stimuli

# Review of the Effectiveness of Transcranial Magnetic Stimulation for Post-traumatic Stress Disorder

*Brain Stimulation*, 2014

Ethan F. Karsen<sup>a,\*</sup>, Bradley V. Watts<sup>a,b</sup>, Paul E. Holtzheimer<sup>a,c</sup>

## **Transcranial magnetic stimulation for posttraumatic stress disorder: an updated systematic review and meta-analysis**

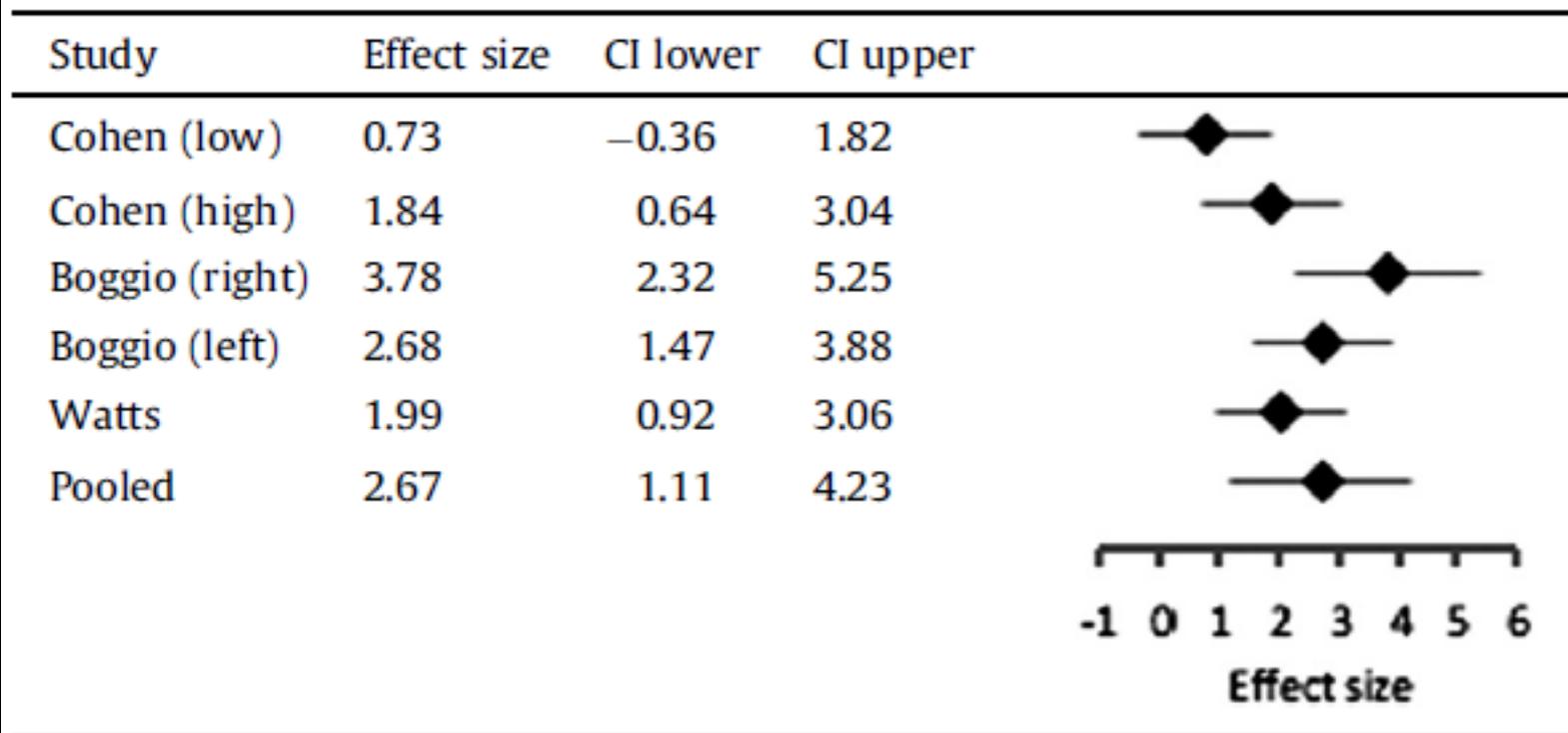
Alisson Paulino Trevizol,<sup>1</sup> Mirna Duarte Barros,<sup>1</sup> Paula Oliveira Silva,<sup>1</sup> Elizabeth Osuch,<sup>2</sup> Quirino Cordeiro,<sup>1</sup> Pedro Shiozawa<sup>1</sup>

*Trends Psychiatry Psychotherapy*, 2016

- Studied since 1998 (mostly small trials)
- Efficacious for PTSD, but:
  - Heterogeneity in parameters:
    - Low vs. high Hz
    - Left vs. right DLPFC / medial PFC
    - Number of pulses/sessions

# TMS for PTSD

Forest plot showing effect size calculated as Hedges  $g$  for TMS on PTSD symptom scales.



CI = confidence interval.

# Recent Studies

- Chart review suggested potential efficacy of **left 5 Hz rTMS**
- Mult-site VA trial of TMS for depression suggested patients with comorbid PTSD did *less well* with **left 10 Hz rTMS**
- Study showing equal efficacy for **10 Hz right and 1 Hz right rTMS** (no sham control)
- Pilot studies showing potential benefit for right **theta-burst stimulation** and **synchronized TMS**

# TMS + Psychotherapy

- Early, small trials showed possible efficacy of TMS when combined with exposure to traumatic stimuli or exposure therapy
- Recent, larger study ( $n \approx 100$ ) showed benefit for active vs. sham **1 Hz right rTMS** applied prior to session of cognitive processing therapy

# TMS for PTSD: Key Points

- TMS is an established and available treatment for **depression**
- TMS for **PTSD** remains *experimental*
  - No clear “best” treatment parameters have emerged
  - Some suggestion that 10 Hz left (used for depression) may not be effective in patients with PTSD
- Currently an area of active investigation both as stand-alone treatment (daily sessions for 4-6 weeks) vs. combined with psychotherapy

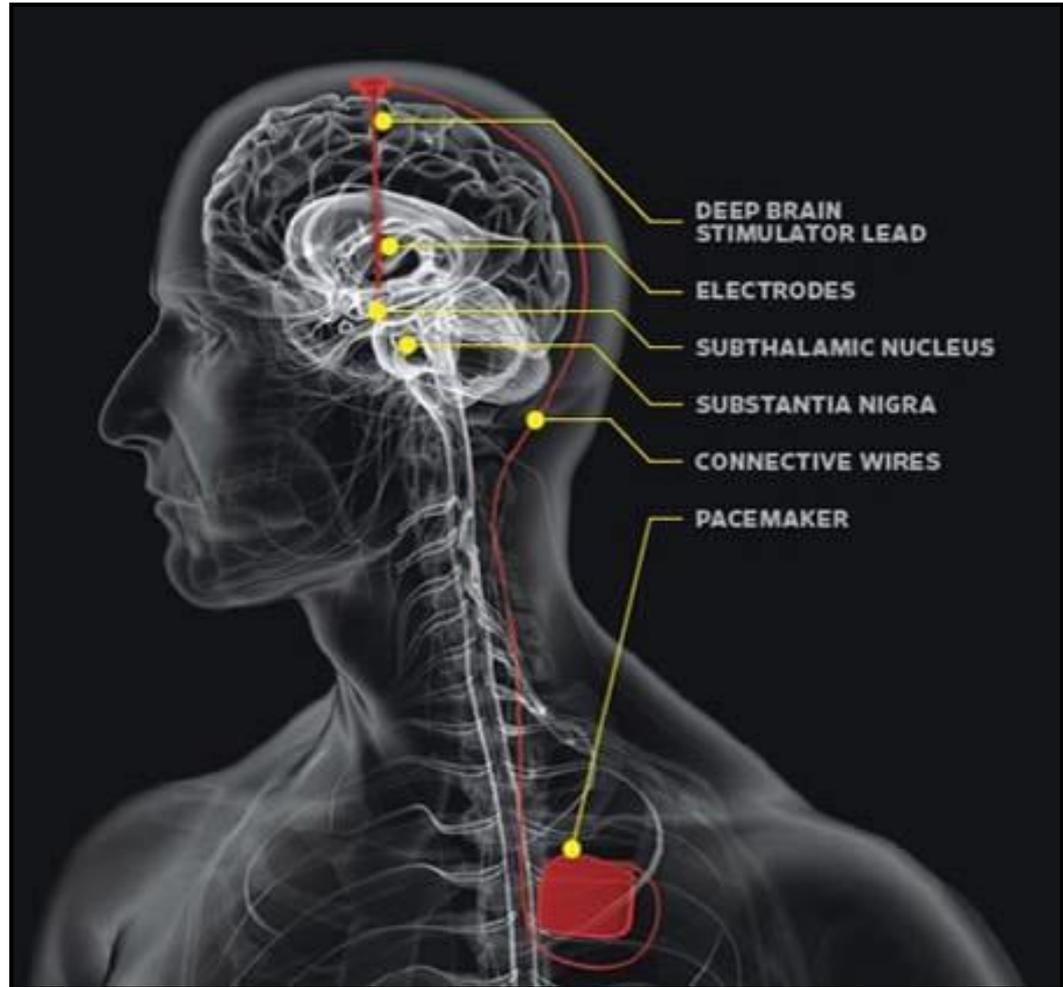
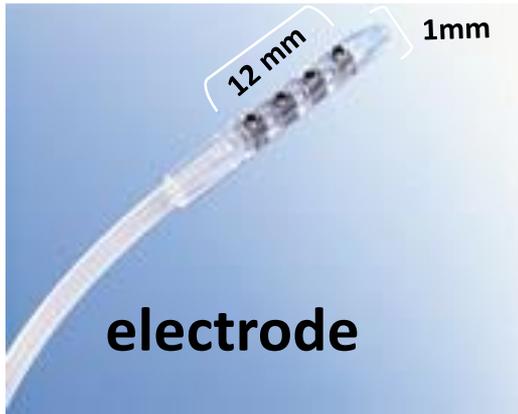
# tDCS for PTSD

- Mixed data on efficacy of tDCS for depression
- Preliminary data that tDCS combined with behavioral strategies (e.g., exposure) may improve PTSD symptoms
- No larger, sham-controlled data available

# CES for PTSD

- CES is “FDA-cleared” for treatment of depression, anxiety, insomnia
  - Common versions: Fisher-Wallace, Alpha-Stim
  - Potentially available within VA
- No high-quality data exist for CES for treatment of any psychiatric disorder
- Open-label pilot study of CES for PTSD ongoing at White River Junction VAMC

# Deep Brain Stimulation (DBS)



# DBS

- Established treatment for medication-refractory Parkinson Disease, Essential Tremor, Dystonia
- Available for treatment of OCD (but limited data)
- Growing but mixed database for treatment of treatment-resistant depression
- Preliminary animal studies suggesting potential benefit in PTSD

# Deep brain stimulation of the basolateral amygdala for treatment-refractory combat post-traumatic stress disorder (PTSD): study protocol for a pilot randomized controlled trial with blinded, staggered onset of stimulation

Ralph J Koek<sup>1,2,9\*</sup>, Jean-Philippe Langevin<sup>2,3</sup>, Scott E Krahl<sup>2,4</sup>, Hovsep J Kosoyan<sup>2,4</sup>, Holly N Schwartz<sup>1,2</sup>, James WY Chen<sup>2,5</sup>, Rebecca Melrose<sup>2,6</sup>, Mark J Mandelkern<sup>2,7,8</sup> and David Sultzer<sup>1,2</sup>

*Trials*, 2014

- First case did very well (Langevin et al., *Biol Psychiatry*, 2016)
- Recruitment ongoing (NCT02091843)
  - Los Angeles VA
  - Male combat veterans 25-70 years old
  - Highly treatment-resistant sample

# SUMMARY

- Focal brain stimulation offers a novel paradigm for treating psychiatric disorders, including PTSD
- Multiple approaches are available that differ in brain regions targeted and invasiveness
- Majority of research has involved TMS:
  - Encouraging results to date
  - Continues to be experimental for PTSD



**THANK  
YOU**





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**Please enter your  
questions in the Q&A box  
and be sure to include your  
email address.**

*The lines are muted to avoid background noise.*



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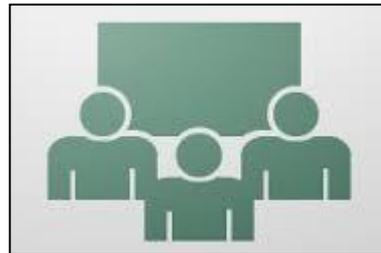
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TRAIN.*



*Listen to the  
lecture.*



*Return to  
TRAIN for  
evaluation.*



*Follow the  
directions to  
print  
certificate.*

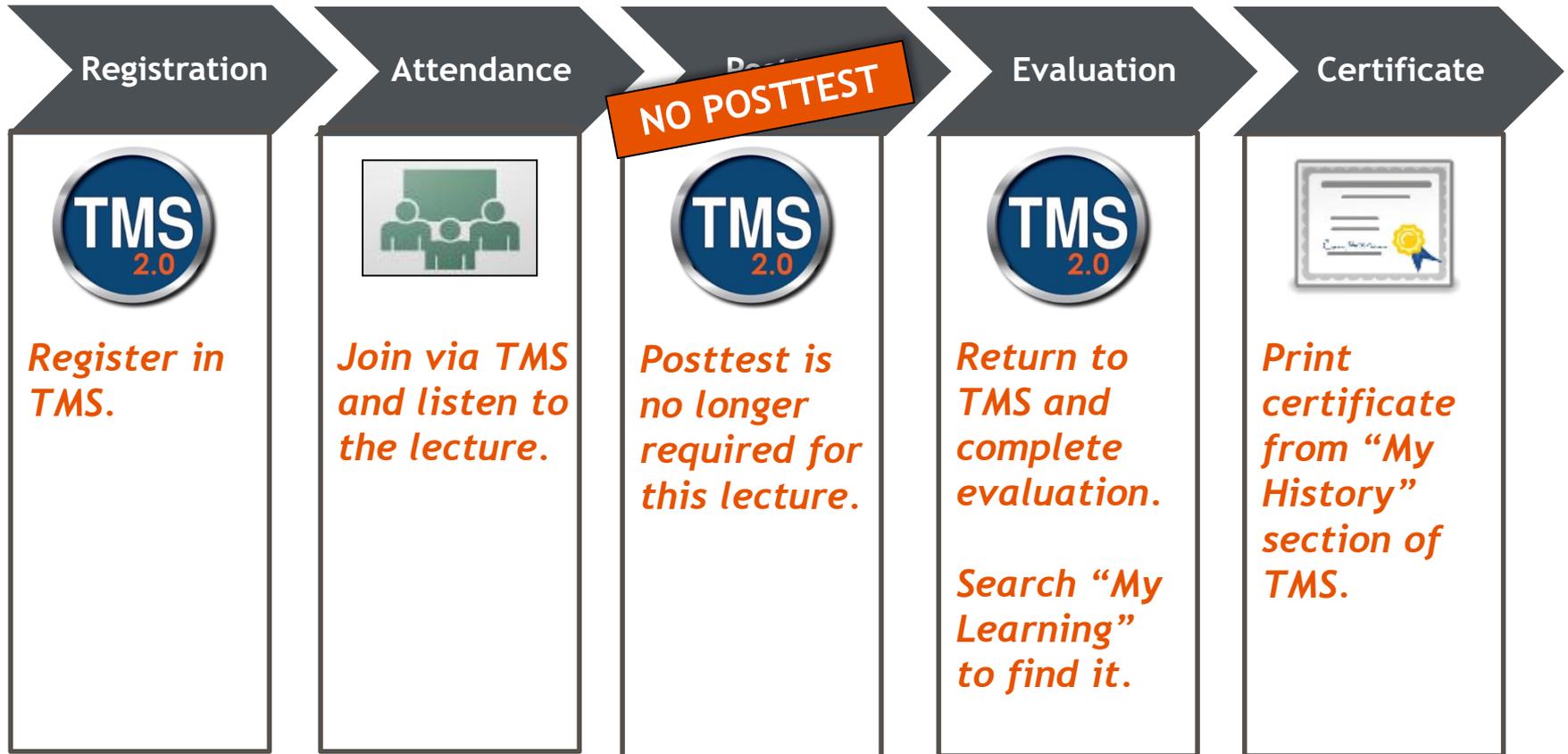
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## CEU Process (for VA employees)





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## UPCOMING TOPICS

***SAVE THE DATE: Third Wednesday of the Month from 2-3PM (ET)***

<b>September 18</b>	<i>Treating PTSD and Cognitive Impairment from Traumatic Brain Injury</i>	Amy Jak, PhD
<b>October 16</b>	<i>Unconventional Interventions for PTSD: State of the Evidence</i>	Paul Holtzheimer, MD
<b>November 20</b>	<i>Addressing Sleep: A Strategy for Symptom Reduction &amp; Suicide Prevention?</i>	Wilfred Pigeon, PhD
<b>December 18</b>	<i>Treating Comorbid PTSD and Borderline Personality Disorder</i>	Melanie Harned, PhD, ABPP
<b>January 15</b>	<i>Dissociation, Somatization, and Other Challenging Presentations of PTSD</i>	Abigail Angkaw, PhD
<b>February 19</b>	<i>Concurrent Treatment of PTSD and SUDs using Prolonged Exposure (COPE)</i>	Sudie Back, PhD

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