Focal Brain Stimulation for PTSD

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Disclosures

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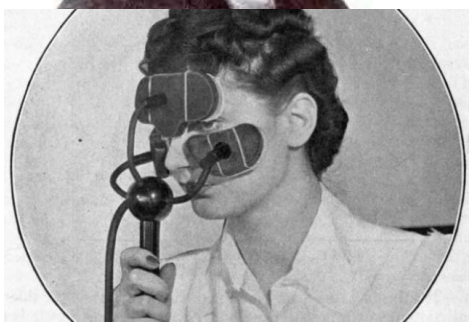
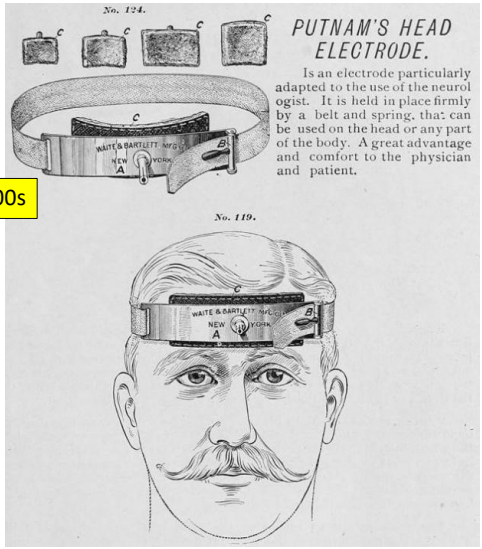
Stock Shareholder/IP: None

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

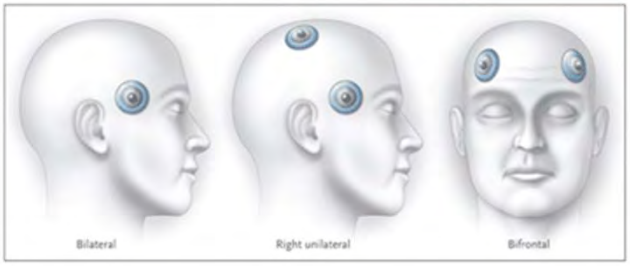
2500-0 BCE



1700s-1900s

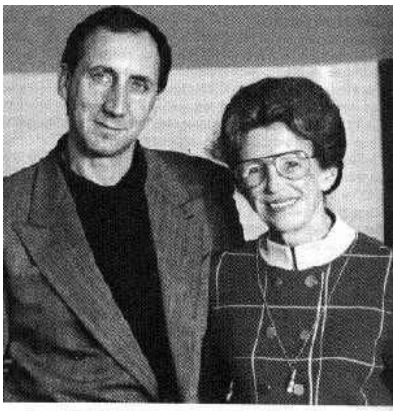

No. 124.
PUTNAM'S HEAD ELECTRODE.
Is an electrode particularly adapted to the use of the neurol ogist. It is held in place firmly by a belt and spring, that can be used on the head or any part of the body. A great advantage and comfort to the physician and patient.
No. 119.

ECT



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

Dr. Margaret Patterson with an early cranial electrotherapy system



Meg with Pete Townshend, after his treatment. 1982

1960s-1980s

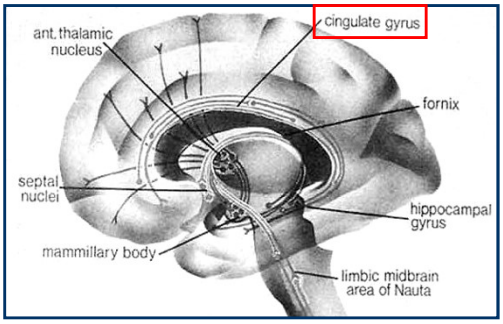
Treatment paradigms

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

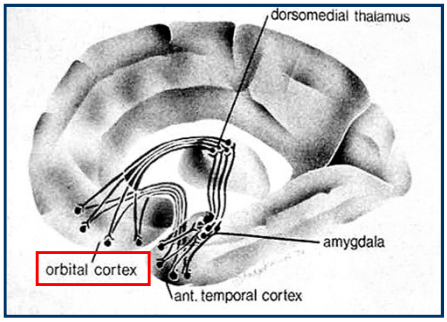
Neural Circuit Paradigm for Tx

- 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



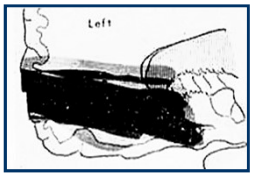
Medial Limbic Circuit



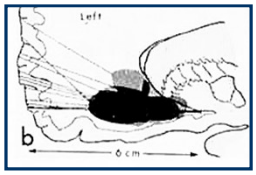
Basolateral Limbic Circuit

Papez JW. *Arch Neurol Psychiatry 38:725-743*, 1937

Surgical Approaches: White Matter Disconnection

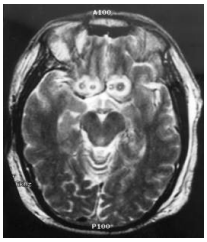


Orbital undercutting

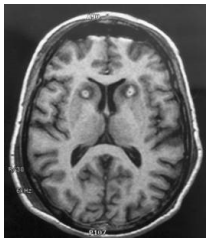


Yttrium subcaudate tractotomy

Cingulo-tractotomy



Subcaudate Tractotomy

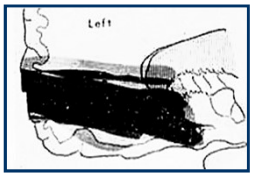


Anterior Capsulotomy

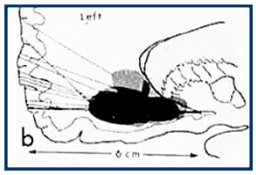
Anterior Cingulotomy

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

Surgical Approaches: White Matter Disconnection

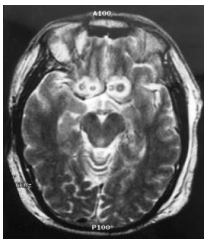


Orbital undercutting

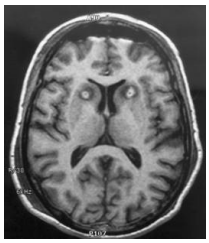


Yttrium subcaudate tractotomy

Cingulo-tractotomy



Subcaudate Tractotomy



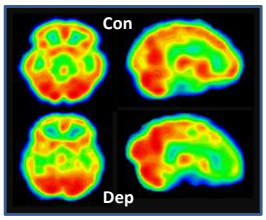
Anterior Capsulotomy

Anterior Cingulotomy

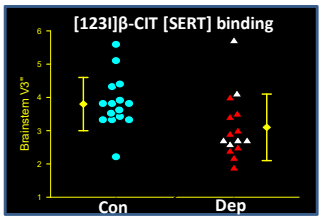
CHALLENGES:

NEED BETTER MODELS

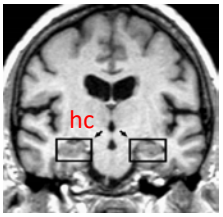
NEED BETTER METHODS



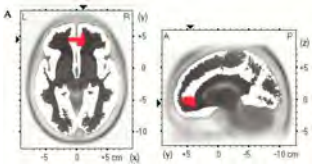
PET/SPECT



Ligand imaging (PET/SPECT)

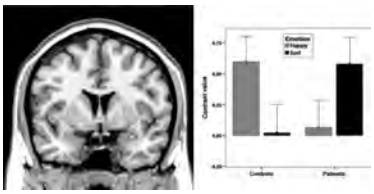


Structural MRI

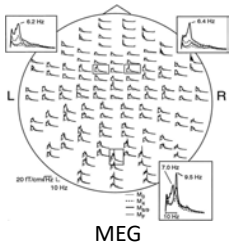


EEG

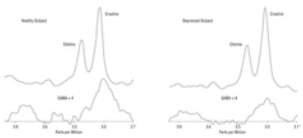
Neuroimaging methods



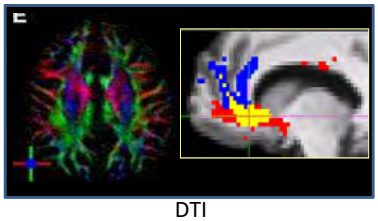
Functional MRI



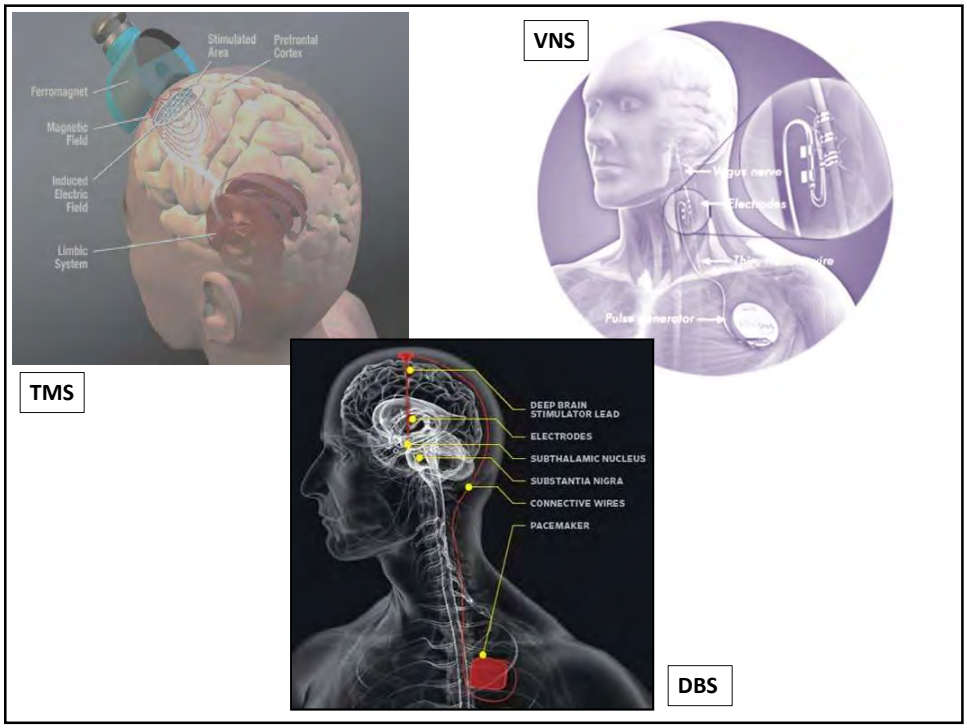
MEG

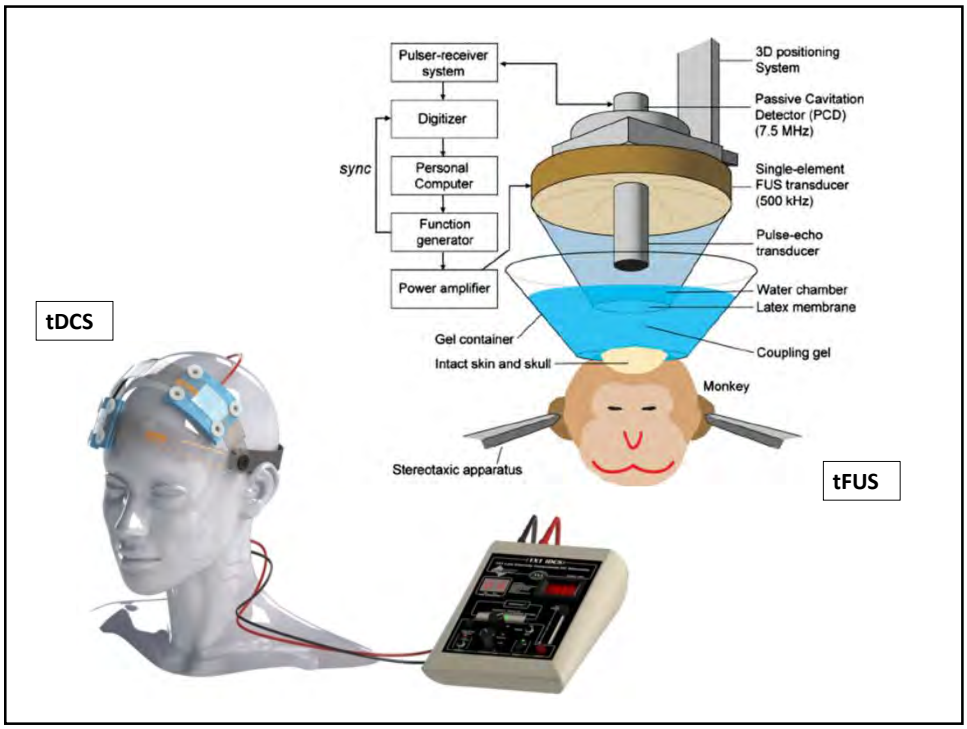


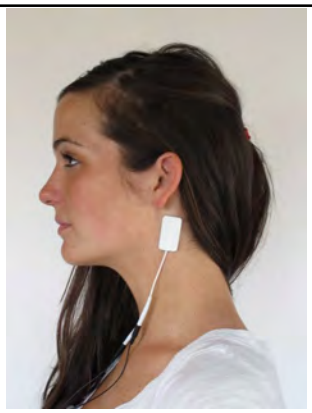
MRS



DTI

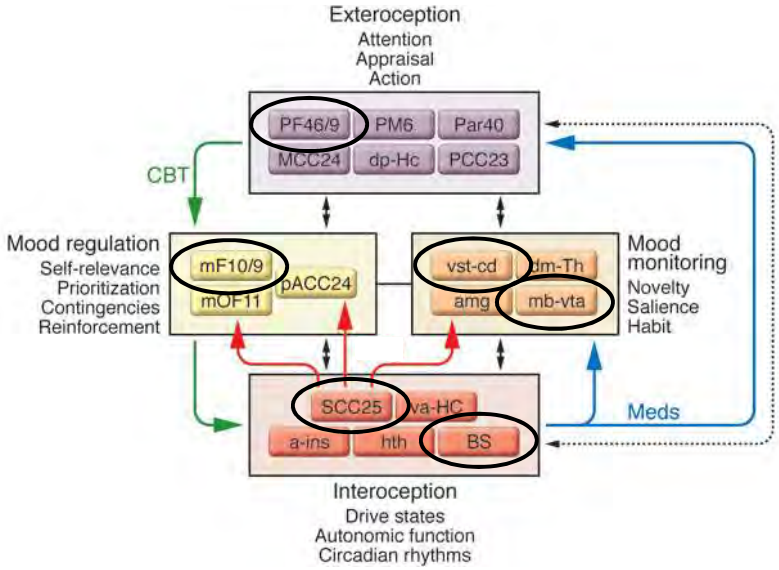

Stimulated Area
Prefrontal Cortex
Ferromagnet
Magnetic Field
Induced Electric Field
Limbic System
TMS
VNS
Vagus nerve
Electrodes
Pulse generator
DEEP BRAIN STIMULATOR LEAD
ELECTRODES
SUBTHALAMIC NUCLEUS
SUBSTANTIA NIGRA
CONNECTIVE WIRES
PACEMAKER
DBS


Pulser-receiver system
Digitizer
sync
Personal Computer
Function generator
Power amplifier
3D positioning System
Passive Cavitation Detector (PCD) (7.5 MHz)
Single-element FUS transducer (500 kHz)
Pulse-echo transducer
Water chamber
Latex membrane
Gel container
Intact skin and skull
Coupling gel
Monkey
Stereotaxic apparatus
tDCS
tFUS



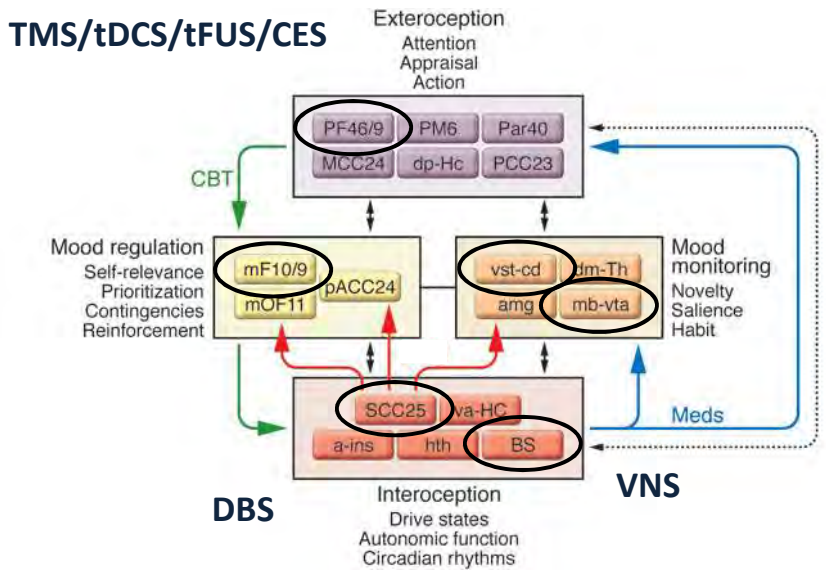
CES (tACS)

Putative "Depression" Network



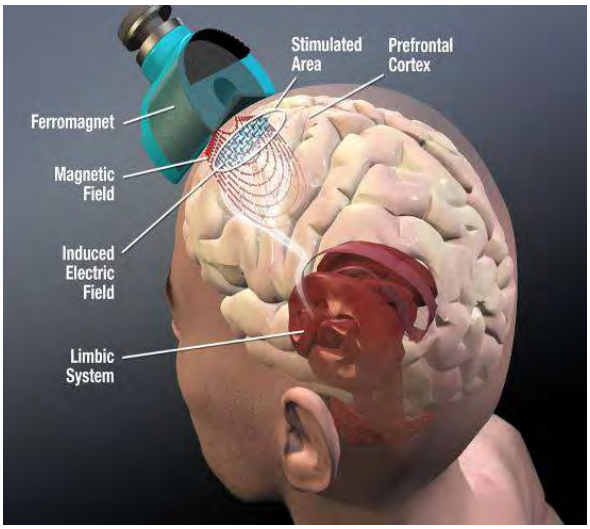
Modified from Mayberg, *J Clin Invest* 2009, 119(4):717-725

Putative "Depression" Network



Modified from Mayberg, *J Clin Invest* 2009, 119(4):717-725

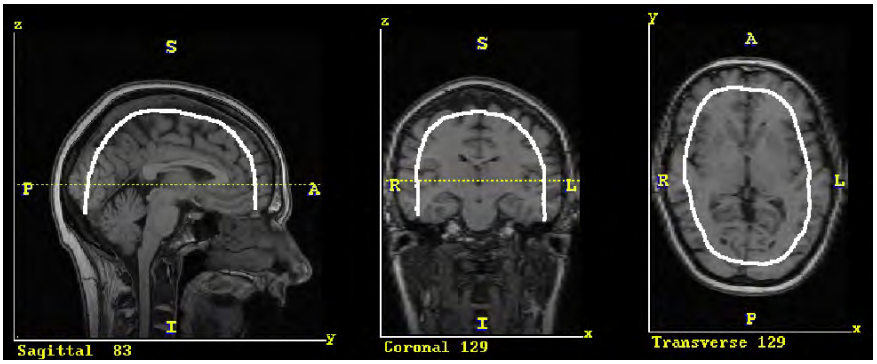
Transcranial Magnetic Stimulation (TMS)



- **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: ≤ 1 Hz
  - Fast/high Hz: ≥ 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**

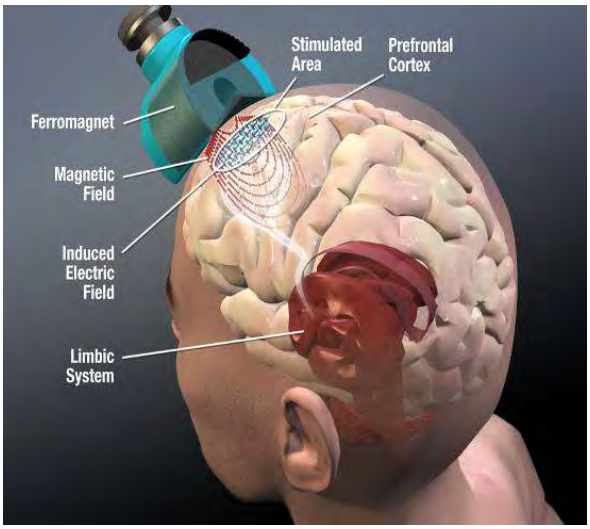
Side effects and contraindications

- 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



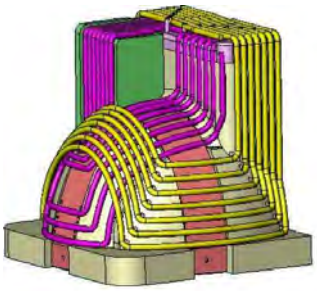
- **Location:**
  - **Left vs. right dorsolateral prefrontal cortex**
- **Parameters:**
  - **Left: 5-20 Hz; right: 1 Hz**
  - **80%-120% motor threshold**
  - **~30-40 min tx**
  - **15-30 txs, daily, over 3-6 weeks**

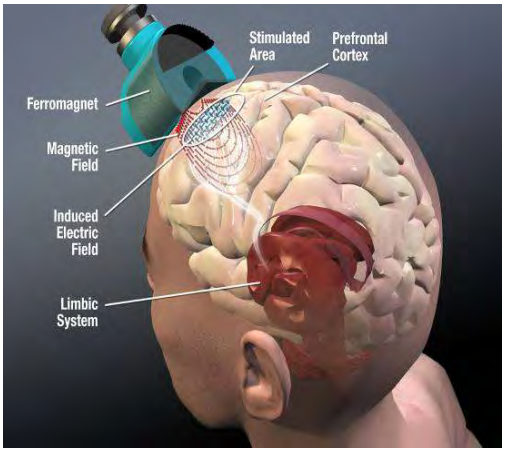
rTMS: Antidepressant Efficacy

- 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

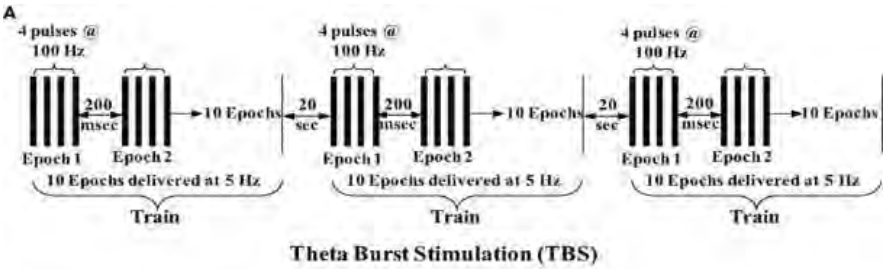
- At least four FDA-approved TMS devices
- Available for tx of depression within VA (TMS Pilot Program)

"Deep" TMS





Theta Burst TMS (TBS)



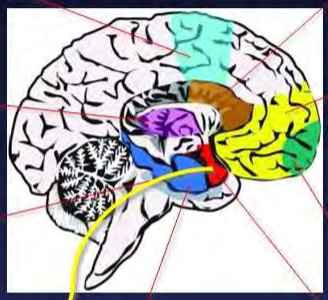
Session length: ~10 min instead of ~40 min

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

From: Mahan AL, Ressler KJ. Trends Neurosci, 2012, 35:24-35.

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

Brain Stimulation, 2014

Ethan F. Karsen[a,*], Bradley V. Watts[a,b], Paul E. Holtzheimer[a,c]

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

Alisson Paulino Trevizol,[1] Mirna Duarte Barros,[1] Paula Oliveira Silva,[1] Elizabeth Osuch,[2] Quirino Cordeiro,[1] Pedro Shiozawa[1]

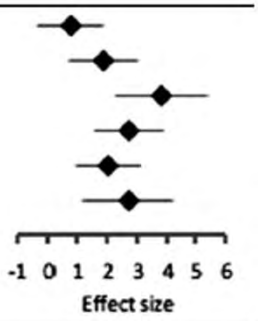
Trends Psychiatry Psychotherapy, 2016

- 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.

Study	Effect size	CI lower	CI upper
Cohen (low)	0.73	−0.36	1.82
Cohen (high)	1.84	0.64	3.04
Boggio (right)	3.78	2.32	5.25
Boggio (left)	2.68	1.47	3.88
Watts	1.99	0.92	3.06
Pooled	2.67	1.11	4.23



CI = confidence interval.

Karsen et al., *Brain Stimulation*, *2014*

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 ≈ 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

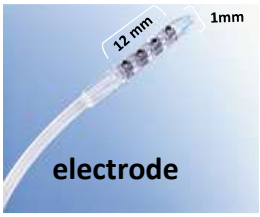
tDCS for PTSD

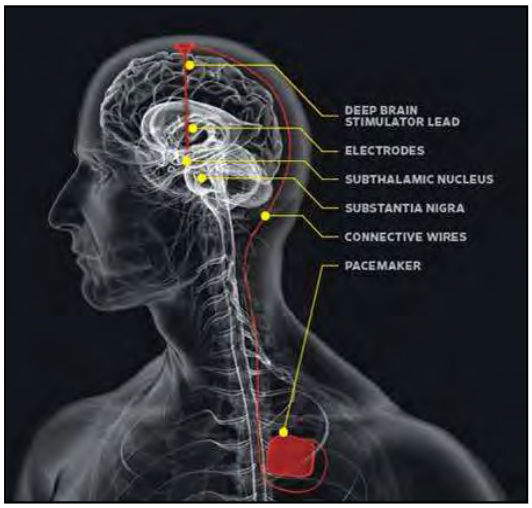
- Mixed data on efficacy of tDCS for depression
- Preliminary data that tDCS combined with behavioral strategies (e.g., exposure) may improve PTSD symptoms
- No larger, sham-controlled data available

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[1,2,9*], Jean-Philippe Langevin[2,3], Scott E Krahl[2,4], Hovsep J Kosoyan[2,4], Holly N Schwartz[1,2], James WY Chen[2,5], Rebecca Melrose[2,6], Mark J Mandelkern[2,7,8] and David Sultzer[1,2]

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 an invasiveness
- Majority of research has involved TMS:
  - Encouraging results to date
  - Continues to be experimental for PTSD

THANK YOU