Focal Brain Stimulation for PTSD

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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.
1700s-1900s

**PUTNAM’S HEAD ELECTRODE.**

Is an electrode particularly adapted to the use of the neurologist. 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.
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

Papez JW. Arch Neurol Psychiatry 38:725-743, 1937
Surgical Approaches: White Matter Disconnection

- **Orbital undercutting**
- **Yttrium subcaudate tractotomy**
- **Cingulo-tractotomy**

**Surgical Approaches:**

- **White Matter Disconnection**
  - **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

CHALLENGES:

NEED BETTER MODELS

NEED BETTER METHODS
Neuroimaging methods

PET/SPECT

Ligand imaging (PET/SPECT)

Structural MRI

EEG

Functional MRI

MEG

MRS

DTI
CES (tACS)
Putative “Depression” Network

Putative “Depression” Network

TMS/tDCS/tFUS/CES

DBS

VNS

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

ANTEROIOR CINGULATE CORTEX
Function: Autonomic functions, cognition
In PTSD: Reduced volume, higher resting metabolic activity

THALAMUS
Function: Sensory relay station
In PTSD: Decreased cerebral blood flow

PREFRONTAL CORTEX
Function:
- Emotional regulation
In PTSD:
- Decreased gray and white matter density
- Decreased responsiveness to trauma and emotional stimuli

PARAHIPPOCAMPAL GYRUS
Function: Important for memory encoding and retrieval
In PTSD: Show stronger connectivity with medial prefrontal cortex; decreases in volume

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

• 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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size</th>
<th>CI lower</th>
<th>CI upper</th>
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</thead>
<tbody>
<tr>
<td>Cohen (low)</td>
<td>0.73</td>
<td>-0.36</td>
<td>1.82</td>
</tr>
<tr>
<td>Cohen (high)</td>
<td>1.84</td>
<td>0.64</td>
<td>3.04</td>
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<tr>
<td>Boggio (right)</td>
<td>3.78</td>
<td>2.32</td>
<td>5.25</td>
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<tr>
<td>Boggio (left)</td>
<td>2.68</td>
<td>1.47</td>
<td>3.88</td>
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<tr>
<td>Watts</td>
<td>1.99</td>
<td>0.92</td>
<td>3.06</td>
</tr>
<tr>
<td>Pooled</td>
<td>2.67</td>
<td>1.11</td>
<td>4.23</td>
</tr>
</tbody>
</table>

Cl = 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)

electrode

IPG
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

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
Oh, thank you so much for helping! We were on our way to terrorize the villagers when my monster just up and died on me... We'd still be stuck here if it wasn't for you.

Yeah, yeah... Another wet-behind-the-ears mad scientist.
Please enter your questions in the Q&A box and be sure to include your email address.

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

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