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.
ECT

Dr. Margaret Patterson with an early cranial electrotherapy system

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

- 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

Subcaudate Tractotomy  Anterior Capsulotomy  Anterior Cingulotomy

PET/SPECT  Ligand imaging (PET/SPECT)  Structural MRI

EEG  Neuroimaging methods  MEG  MRS  DTI

Neuroimaging methods
Paul Holtzheimer, MD, MSCR (NCPTSD):
Focal Brain Stimulation for PTSD

MIRECC Presents:
https://www.mirecc.va.gov/visn20/
Putative “Depression” Network

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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

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

Ethan F. Karsen\textsuperscript{a}, Bradley V. Watts\textsuperscript{a,b}, Paul E. Holtzheimer\textsuperscript{a,c}

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

Aliison Paulino Trevizol,\textsuperscript{1} Mirna Duarte Barros,\textsuperscript{1} Paula Oliveira Silva,\textsuperscript{1} Elizabeth Osuch,\textsuperscript{1} Quirino Cordeiro,\textsuperscript{1} Pedro Shinzawa\textsuperscript{1}

TMS for PTSD

- 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

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https://www.mirecc.va.gov/visn20/
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

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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

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**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**

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