Brain Stimulation Therapies in Neuropsychiatry

C. Edward Coffey MD
Professor of Psychiatry and of Neurology
Chair, Department of Psychiatry
Henry Ford Health System

Depression and the Brain in Context

Biological Vulnerability  Exogenous Stressors

gender  family history  temperament
genetics  pre-natal insults

Psychotherapy  Medication
ECT, rTMS, VNS  DBS?

Mood Regulatory Circuits

homeostasis
post-natal insults
early abuse
life events
medical illness

Re-stabilized  De-stabilized

Depressive Episode

Phenotype (subtypes?)

Limbic-Cortical Model of Depression
Brain Stimulation in Neuropsychiatry

History

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Brain Stimulation in Neuropsychiatry

History

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Brain Stimulation in Neuropsychiatry

Brain Stimulation Techniques

- **Transcranial Electrical Stimulation (TES)**
- ECT*: Electrodes (2) to scalp
- FEAST: Electrode montage to scalp
- Anesthesia Only: Isoflurane, Ketamine IV administration of drug
- Direct Current Stimulation: Anode and cathode to scalp
- CES*: Electrodes to ears
- Transcranial Magnetic Stimulation (TMS): Magnetic field to scalp
- rTMS*: and related procedures
- MST: Magnetic field to scalp
- Implanted Electrical Stimulation:
  - VNS*: Electrodes to L vagus nerve
  - DBS*: Electrodes implanted in brain
  - ICS: Electrodes implanted on cortex

Brain Stimulation in Neuropsychiatry

Electroconvulsive Therapy (ECT)

- The “Gold Standard”
- FDA “approved” for depression, mania, and catatonia
- Technically complex; anesthesis, seizure, logistics
- Response rates higher in AMCs than in community
- Cognitive side effects; Stigma, legal assault
- Quasi-focal, bidirectional stimulation (BT vs. RUL vs. BF)

Spectral Indices Over Entire Seizure

Effects Of ECT Type

- **2.2 - 5 Hz**
  - Sine/BL: 450µV
  - Pulse/BL: 730µV
  - Pulse / Right UL: 550µV
  - Clinical Response: Marked

- **18.2 - 30 Hz**
  - Peak Spike Amplitude (µV):
    - 730µV
    - 550µV
    - 450µV
    - 275µV
  - Clinical Response: Marked, Marked, Marked, Slight
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Focal Electrically Administered Seizure Therapy (FEAST)

- Enhanced spatial targeting of ECT stimulus
- Relies on unidirectional stimulus (anode-cathode) and novel electrode montage
- In primates, induces a variety of seizure types (focal to generalized)
- Fewer cognitive side effects?
- Human studies underway

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Isoflurane Deep Anesthesia

- Superficial analogy between EEG suppression from anesthesia vs. ECT
- Open uncontrolled clinical series report mixed results in patients with depression following deep isoflurane anesthesia 2x/week for three weeks (burst suppression EEG)

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Ketamine Anesthesia and NMDAR Signaling

- Ketamine (NMDA antagonist) anesthesia facilitates ECT
- Altered glutamate signaling in depression, and NMDA receptor may modulate effects of antidepressants
- Ketamine has antidepressant activity in animal models of depression
- Two small RCTs of ketamine in patients with depression found rapid (110 mins) and robust therapeutic effects (70% response)
- Safety of repeated use unknown!
Brain Stimulation in Neuropsychiatry
Transcranial Direct Current Stimulation

- Neuromodulatory (changes resting membrane potential, no AP); anodal excites, cathodal inhibits
- Very safe; relatively non-focal
- RCT of left DLPFC anodal tDCS (1 mA for 20 min for 5 alternated days) produced 40% response rate in 10 patients with major depression (Fregni 2006)
- Other studies in pain, stroke, Parkinson’s disease

Brain Stimulation in Neuropsychiatry
Principle Features of tDCS

- CES is FDA approved (1979) for treatment of insomnia, depression, and anxiety
- A few small RCTs has found some evidence of efficacy for CES in depression (r effect size 0.57)
- Minimal side effects (headache, skin irritation, light-headedness)

Alpha-Stim Stress Control System
### Brain Stimulation Techniques

**Transcranial Electrical Stimulation (TES)**
- **ECT**
- **FEAST**
- **Direct Current Stimulation**
  - **tDCS**
  - **CES**

**Transcranial Magnetic Stimulation (TMS)**
- **rTMS**
- **MST**
- **Implanted Electrical Stimulation**
  - **VNS**
  - **DBS**
  - **ICS**

#### Brain Stimulation in Neuropsychiatry

**Transcranial Magnetic Stimulation (TMS)**
- Uses electricity to induce powerful, pulsed magnetic fields which pass unimpeded through skull to induce current in underlying neurons
- Single- and paired-pulse TMS can measure variety of cortical neuronal functions such as inhibition (impaired in some NP disorders?), plasticity, and connectivity

**rTMS Therapy**
- rTMS can activate (high freq) or inhibit (low freq) cortical activity
- Non-invasive, safe
- A probe of cognition?
- Approved for use in Canada, Israel, and Australia
- “Cleared” by FDA 10.8.08, for adults with MDD refractory to one AD trial

**Anesthesia Only**
- **Isoflurane**
- **Ketamine** IV administration of drug

**Electrodes montage to scalp**
- Anode and cathode to scalp
- Electrodes to ears
- Electrodes to L. vagus nerve
- Electrodes implanted in brain
- Electrodes implanted on cortex
**Prefrontal TMS Affects Mood Circuits in Depressed Adults**

Pooled results of 1 Hz 100% MT TMS for 20 seconds minus rest, 1.5 T BOLD fMRI, 3 adults with depression, z>3.09 for display

Li, Nahas et al, Work in Progress, MUSC

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**Brain Stimulation in Neuropsychiatry**

**Efficacy of rTMS in Depression**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Standardised mean diff. (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egger et al. 2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garcia-toro</td>
<td>0.84 (0.05, 1.63)</td>
<td></td>
</tr>
<tr>
<td>Januel</td>
<td>1.49 (0.62, 2.36)</td>
<td></td>
</tr>
<tr>
<td>Avery</td>
<td>0.82 (0.32, 1.31)</td>
<td></td>
</tr>
<tr>
<td>Rossini</td>
<td>0.63 (0.23, 1.03)</td>
<td></td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>0.59 (0.02, 1.16)</td>
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</tbody>
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**TMS Therapy in Major Depression**

**Multi-Site RCT (O’Reardon et al 2007)**

- **Phase I**
  - Drug-Free Lead-In 7-20 days
- **Phase II**
  - Acute Treatment Phase 6 weeks
- **Phase III**
  - Taper Phase 3 weeks

- **Neurostar TMS Therapy (n=155)**
  - 120% MT
  - 10 pulses per second
  - 4 sec on-time/26 sec off-time
  - 3000 pulses/session

- **Sham (n=146)**
  - <10% field exposure at cortex

- **Primary Efficacy @ 4 weeks**
- **Secondary Efficacy @ 6 weeks**
- **Durability of Effect @ 9 weeks**
TMS Therapy in Depression
Multi-Site RCT (O’Reardon et al 2007)

TMS Therapy in Depression
Open-Label Extension Trial (Avery et al 2008)

TMS Therapy in Major Depression
Many Unanswered Questions

- Multiple Technical Factors
  - Stimulation site (L PFC, R PFC, both)
  - rTMS parameters (frequency, intensity, waveform, number)
  - Duration of treatment course
- Predictors of Non-response?
  - Age, psychosis, episode duration, treatment resistant
- Less cost-effective than ECT (resource intensive)
- NIMH multi-center trial underway
rTMS in Neuropsychiatry
New Methodologies for rTMS

- Theta burst stimulation
- Repetitive paired-pulse TMS
- Quadripulse TMS
- Controllable pulse shape TMS
- Deep brain TMS (Roth et al 2007)

Brain Stimulation in Neuropsychiatry
Magnetic Seizure Therapy (MST)

- Uses intense rTMS to induce a therapeutic seizure under anesthesia
- MST produces more focal (less deep) stimulation (primates) and more focal seizures (primates, humans)
- In theory, may produce fewer cognitive side effects than ECT

Brain Stimulation in Neuropsychiatry
Magnetic Seizure Therapy (MST)

- In primates, MST has benign acute cognitive side effects and less intense ictal and post-ictal EEG effects (except delta), vs. BT ECS
- Small, open studies in humans (n~55) find improved orientation, but perhaps less efficacy, vs. BT ECT. RCTs underway.
- Technically complex, requires general anesthesia and more powerful devices
Brain Stimulation in Neuropsychiatry

Brain Stimulation Techniques

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Vagus Nerve Stimulation (VNS)

- Modulation of brain systems via electrical stimulation of left vagus nerve in neck

- FDA approved as add-on treatment for partial epilepsy (July, 1997)
- Response: ~25% at 3 months, ~40% at 1-3 years
- Side effects: voice changes (68%); cough, dyspnea, neck pain, dysphagia (~25%); low discontinuation rates
- Obviates adherence issues
**Tone and VNS on Same Image**

Visceral/Emotional Brain

- 9 Subjects, p<0.01, extent p<0.05 for Display

Visual Brain

- VNS - red, Tone-yellow

Auditory Brain

**Brain Stimulation in Neuropsychiatry**

Efficacy of VNS in Refractory Depression

- Remission
- Response

<table>
<thead>
<tr>
<th>Time</th>
<th>Open Trial VNS + TAU (n = 59)</th>
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<tbody>
<tr>
<td>10 weeks</td>
<td>Remission</td>
</tr>
<tr>
<td>1 year</td>
<td>Response</td>
</tr>
<tr>
<td>2 years</td>
<td>Remission</td>
</tr>
</tbody>
</table>

**Brain Stimulation in Neuropsychiatry**

VNS “Pivotal Study” Design (2005)

<table>
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<tr>
<th>Phase</th>
<th>VNS + TAU</th>
<th>Sham Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>≤ 45 days</td>
<td>n = 112</td>
</tr>
<tr>
<td>Implant</td>
<td>2 weeks</td>
<td>n = 110</td>
</tr>
<tr>
<td>Stimulus Response</td>
<td>Fixed Dose VNS 2 weeks</td>
<td></td>
</tr>
<tr>
<td>8 weeks</td>
<td>Remission</td>
<td></td>
</tr>
<tr>
<td>Open VNS Trial</td>
<td>24 months</td>
<td></td>
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Brain Stimulation in Neuropsychiatry

VNS Brain Stimulation Laboratory

And Center for Advanced Imaging Research
Brain Stimulation in Neuropsychiatry
Efficacy of VNS in Refractory Depression

Brain Stimulation in Neuropsychiatry
Vagus Nerve Stimulation (VNS)

- FDA approved for treatment-refractory major depression in adults (7/2005)
- 2006 bad publicity
- On 2/5/07, CMS made a “national non-coverage determination” for VNS, as “not reasonable and necessary for treatment-resistant depression”

Brain Stimulation in Neuropsychiatry
The Challenge of Industry Relations

Our Conflicted Medical Journals
July 23, 2006
The New York Times
An even more egregious set of events occurred at Neuropsychopharmacology, which recently published a favorable assessment of a controversial new treatment for depression resistant to conventional therapies. Left unmentioned was that eight of the nine authors serve as consultants to the company that makes the device used in the therapy. The ninth worked directly for the company. Just to make things particularly incestuous, the lead author of the study is the journal’s editor and a consultant to the company. He has been accused in the past of promoting therapies in which he had a financial stake.

Medical Journal Editor to Quit in Wake of Disclosure Oversight

The editor of the journal Neuropsychopharmacology is stepping down following a flap over the medical journal’s failure to disclose that the authors of a paper reviewing a new treatment for depression had financial ties to the treatment’s developer.
Brain Stimulation in Neuropsychiatry
Implanted Cortical Stimulation (ICS)

Kopell et al, Northstar Neuroscience
- Multicenter, RT (single-blind) of ICS (BA 9/46) vs. sham for depression (n=11)
- Over 52-week follow-up, 36% responded and 18% remitted

Brain Stimulation in Neuropsychiatry
Deep Brain Stimulation (DBS)

- FDA approved for refractory parkinsonism and tremor (1997)
- Side effects: hemorrhage, infection, seizure, mood changes
- Trials in OCD (HDE in 2009), MDD

Prototype Disorder: Parkinson's Disease

1. pathology
   - healthy SN, PD

2. chemistry
   - Measured brain regions

3. DBS
   - Ablation

4. More than 1 effective target
DBS Bilateral STN
tremor

DBS of Pedunculopontine Nucleus
OFF then ON

DBS in Cervical Dystonia
Left and Right DBS OFF; Left and Right DBS ON

2 years post-op
DBS OFF

2 years post-op
DBS ON
Psychiatric Effects of Stimulation in the Subthalamic Area

Depression, anxiety (Bejjani et al, NEJM, 1999)

Euphoria, Laughter, Mania

• In patients with severe OCD, psychosurgery relatively effective (10% - 60% improvement), but has adverse effects
• DBS (vc/vs) also effective and perhaps safer (but not benign), and was also associated with improved mood in some patients

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Psychosurgery and DBS in OCD

Malone et al (2009)

• Ventral aspect of ant. limb of internal capsule (n=15)
• Response/ remission rates 40%/20% at 6 mths; 53%/40% at last f/u (0.5 – 4 yrs)
• Generally well tolerated

Brain Stimulation in Neuropsychiatry
DBS for Depression
Brain Stimulation in Neuropsychiatry

DBS for Depression

Schlaepfer (2008)

- Nucleus accumbens
- Stimulation produced immediate improvement in 3 patients with depression, which worsened when stimulation turned off
- PET showed changes in fronto-striatal networks

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DBS for Depression

Mayberg (2008)

Subgenual cingulate (BA 25)
DBS in 20 patients

<table>
<thead>
<tr>
<th></th>
<th>1 mo</th>
<th>6 mo</th>
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<tbody>
<tr>
<td>Response</td>
<td>35%</td>
<td>60%</td>
</tr>
<tr>
<td>Remission</td>
<td>10%</td>
<td>35%</td>
</tr>
</tbody>
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Benefits “largely maintained” at 12 mths

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DBS for Depression

Mayberg (Toronto/Emory)

- DBS was associated with specific changes in rCMR localized to cortical and limbic circuits implicated in pathogenesis of depression
- Mechanism unknown – predominantly stimulatory, with chronic driving (+ or -) of remote nodes?
- Authors have patented the stimulus location.
Light-sensitive gates are implanted into neurons using viral vectors, and then cell activity is controlled by optical fibers (for deep regions) or LED’s mounted on scalp.