Noninvasive Neuromodulation in Psychiatric Treatment:

Current and Developing

Sarah H. Lisanby, MD
J.P. Gibbons Professor and Chair
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- Benefits
- Risks
- Critical knowledge gaps and needs for future work
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- Benefits
  - Unparalleled efficacy

![ECT Device]

Source: STAR-D Trial
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- **Benefits**
  - Unparalleled efficacy
  - Rapidly resolves suicide risk

Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- Benefits
- Risks
  - Memory loss
    - Reduced with unilateral electrode placement

Lisanby et al. Arch Gen Psych 2000;57:381
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- **Benefits**
- **Risks**
  - **Memory loss**
    - Reduced with unilateral electrode placement, and
    - Ultrabrief pulse width

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![Graph showing Amnesia Score (z) for Standard Pulse and Ultra-Brief Pulse](image)

- **Standard Pulse**
  - 1-2 ms
- **Ultra-Brief Pulse**
  - 0.25-0.3 ms

Sackeim et al. Brain Stimulation 2008;1:71-83
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- Benefits
- Risks
- Critical knowledge gaps and needs for future work
  - Novel strategies to protect memory
    - Magnetic Seizure Therapy
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- Benefits
- Risks
- Critical knowledge gaps and needs for future work
  - Novel strategies to protect memory
    - Magnetic Seizure Therapy
      - More focal Electric fields in brain

Lee et al. EMBC 2014
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- Benefits
- Risks
- Critical knowledge gaps and needs for future work
  - Novel strategies to protect memory
    - Magnetic Seizure Therapy
      - More focal Electric fields in brain
      - Superior cognitive outcomes

McClintock et al. ACNP 2012
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- Benefits
- Risks
- Critical knowledge gaps and needs for future work
  - Novel strategies to protect memory
  - Deeper understanding of mechanisms of action of seizures
- Remains the most potent antidepressant and suicide prevention strategy currently FDA approved
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- Benefits
  - Antidepressant efficacy

O’Reardon et al. Biol Psychiatry 2007
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- **Benefits**
  - Antidepressant efficacy
  - Tool to target illness-related circuits

Insel. Scientific American. 2010
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- **Benefits**
  - Antidepressant efficacy
  - Tool to target illness-related circuits
  - Lacks amnesia seen with ECT
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- **Benefits**
- **Risks**
  - Hearing loss / tinnitus
  - Seizure
    - Role of concomitant medications
    - Medical comorbidities
    - Substance use disorders
    - Vulnerable populations
      - seizure threshold lower in children, seizure risk higher in autism and after traumatic brain injury
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- Benefits
- Risks
- Critical knowledge gaps and needs for future work
  - Optimal dosage
    - Spatial distribution
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- Benefits
- Risks
- Critical knowledge gaps and needs for future work
  - Optimal dosage
    - Spatial distribution

Deng, Peterchev and Lisanby, 2008
Wide Variety of Coil Designs

Deng, Lisanby, Peterchev. Brain Stim 2013
Wide Variety of Coil Designs

Wide Variety of E-field Spatial Spread

Deng, Brain Stim 2013
New approaches to shape field through coil design

- Single source multi-coil array
- Each loop is neighbored by a loop with current in the opposite direction, permitting field cancellation

Gomez et al. IEEE Transactions on Biomedical Engineering. 2013
New approaches to shape field through coil design

- Single source multi-coil array
- Each loop is neighbored by a loop with current in the opposite direction, permitting field cancellation
- Engineering challenges in implementation

Gomez et al IEEE Transactions on Biomedical Engineering. 2013
New approaches to shape field through coil design

- Cervel Neurotech Deep Shaped-Field repetitive transcranial magnetic stimulator (DSF-rTMS)
  - NCT01431001

- Tal Low Field Magnetic Stimulation (LFMS)
  - NIMH–RAPID, NCT01654796
New approaches to shape field through coil design

- Cervel Neurotech Deep Shaped-Field repetitive transcranial magnetic stimulator (DSF-rTMS) - NCT01431001
- Tal Low Field Magnetic Stimulation (LFMS)
  - NIMH–RAPID, NCT01654796
- NeoSync EEG Synchronized TMS - NCT01370733

Deng et al. Brain Stimulation 2013
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- Benefits
- Risks
- Critical knowledge gaps and needs for future work
  - Optimal dosage
    - Spatial distribution
    - Temporal characteristics
  - Pulse shape

Conventional TMS

cTMS

Pulse width control

Directionality control

Peterchev, Jalinous, & Lisanby 2008
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- Benefits
- Risks
- Critical knowledge gaps and needs for future work
  - Optimal dosage
    - Spatial distribution
    - Temporal characteristics
      - Pulse shape
      - Train parameters
        » Frequency, duration, directionality
Low Frequency Right versus High Frequency Left for Depression

- 8 Randomized Controlled Trial, 249 patients
- No detectable difference between low or high frequency
- Implications for practice as low frequency has lower seizure risk than high frequency

Chen et al. Psychiatry Research. 2013

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Höppner 2003</td>
<td>5</td>
<td>10</td>
<td>3</td>
<td>10</td>
<td>6.8%</td>
<td>2.33 [0.37, 14.61] 2003</td>
</tr>
<tr>
<td>Fitzgerald 2003</td>
<td>3</td>
<td>20</td>
<td>4</td>
<td>20</td>
<td>15.5%</td>
<td>0.71 [0.14, 3.66] 2003</td>
</tr>
<tr>
<td>Stern 2007</td>
<td>4</td>
<td>10</td>
<td>6</td>
<td>10</td>
<td>16.4%</td>
<td>0.44 [0.07, 2.66] 2007</td>
</tr>
<tr>
<td>Fitzgerald 2007</td>
<td>3</td>
<td>15</td>
<td>2</td>
<td>11</td>
<td>8.4%</td>
<td>1.13 [0.15, 8.21] 2007</td>
</tr>
<tr>
<td>Rossini 2008</td>
<td>21</td>
<td>32</td>
<td>24</td>
<td>42</td>
<td>32.5%</td>
<td>1.43 [0.55, 3.71] 2008</td>
</tr>
<tr>
<td>Fitzgerald 2009</td>
<td>7</td>
<td>16</td>
<td>5</td>
<td>11</td>
<td>15.2%</td>
<td>0.93 [0.20, 4.37] 2009</td>
</tr>
<tr>
<td>Eche 2012</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>8</td>
<td>5.2%</td>
<td>2.00 [0.22, 17.89] 2012</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total (95% CI)</th>
<th>109</th>
<th>112</th>
<th>100.0%</th>
<th>1.15 [0.65, 2.03]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total events</td>
<td>47</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 2.51, df = 6 (P = 0.87); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.47 (P = 0.64)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- Benefits
- Risks
- Critical knowledge gaps and needs for future work
  - Optimal dosage
  - Optimal patient selection
    - Other indications
      - Anxiety Disorders
        » OCD, PTSD
      - Addictions
      - Cognitive enhancement
        » TBI
**Future Indications Under Investigation:**

**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>
</tr>
</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>
</tr>
<tr>
<td>Boggio (right)</td>
<td>3.78</td>
<td>2.32</td>
<td>5.25</td>
</tr>
<tr>
<td>Boggio (left)</td>
<td>2.68</td>
<td>1.47</td>
<td>3.88</td>
</tr>
<tr>
<td>Watts</td>
<td>1.99</td>
<td>0.92</td>
<td>3.06</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td><strong>2.67</strong></td>
<td><strong>1.11</strong></td>
<td><strong>4.23</strong></td>
</tr>
</tbody>
</table>

- Both low and high frequency effective

Cl = confidence interval.
Non-Invasive Neuromodulation Devices FDA Approved for Therapeutic Use in Psychiatry

- Benefits
- Risks
- Critical knowledge gaps and needs for future work
  - Optimal dosage
  - Optimal patient selection
  - Concomitant therapies
    - Pharmacological
    - Nonpharmacological/behavioral
Non-Invasive Neuromodulation in Development for Psychiatric Treatment

- Benefits
  - Evidence for antidepressant effects

Brunoni et al. JAMA Psychiatry 2013
Non-Invasive Neuromodulation in Development for Psychiatric Treatment

• Benefits
• Risks
  – Excellent safety profile
• Critical knowledge gaps and needs for future work
  – Mechanisms of action and optimizing dosimetry in space and time
Are we asking the right question?

How does it work?

Extracellular Currents

Endogenously Generated  Exogenously Applied

Neural oscillations – epiphenomenon or signal?
Emerging role of abnormal neural oscillations in psychiatric disorders
Are we asking the right question?

HOW DOES IT WORK?

Extracellular Currents

Endogenously Generated  Exogenously Applied

- Enhancement
- Suppression

Frohlich & Schmidt. Frontiers in Human Neuroscience 2013
Conclusions

- **Spatial** maps of neurocircuitry underlying disorders have guided spatial targeting for depression, but
- **Temporal** targeting is presently lacking, but of great potential impact
- Understanding the interaction between *endogenous* neural dynamics underlying psychiatric disorders and *exogenously* applied electrical currents represents a key knowledge gap in the development noninvasive neuromodulation for psychiatric disorders.
The Future for Devices in Psychiatry

“Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.”

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**Williams Ward** Attendings and Nursing

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- U01 MH084241 (PIs: Kellner and Lisanby)
- K01 AG031912 (PI: Luber, Mentor: Lisanby)
- R21 EB00685 (PIs: Lisanby & Peterchev)
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