Neuroscience and Clinical Applications of Magnetic Brain Stimulation

Dhakshin Ramanathan MD., PhD
Assistant-Professor-in-Residence, UCSD
Department of Psychiatry
Co-Director (With Jyoti Mishra)
Neural Engineering and Translation Labs
Neuroscience 101

1 Human Brain

~86 Billion Neurons

>86 Trillion connections
One of the main jobs of a neurons is to carry bits of information from one place to another.
Neuroscience 101 – Neurons are Chemical

- Neurons use chemicals (neurotransmitters) to communicate.
- Most psychiatric medications act (chemically) at the synapse.
Neuroscience 101 – Neurons Are Electric

Neurons use electricity to carry signals from one place to another.
Neuroscience 101: Brain Recordings

Synchronized Neural Activity Can Be Measured From Outside the Skull (EEG or MEG)
Neuroscience 101: Brain Recordings

And can also be measured using imaging tools (mostly fMRI)
Neuroscience 101: Brain Recordings

These Measures Are A Bit Like Estimating Commerce in the US by Measuring Light – Useful, but Incomplete
Brain Stimulation 101

Big Question 1: Instead of Changing the Chemistry of the Brain, Can We Directly Activate Neurons Electrically?
Brain Stimulation 101 - History

Neurosurgeon Wilder Penfield (1891 – 1976) – Brain stimulation could evoke movements and sensations
When the electrode was applied in gray matter on the cut face of the temporal lobe at point 23, the patient observed: "I hear some music." Fifteen minutes later, the electrode was applied to the same spot again without her knowledge."I hear music again," she said. "It is like radio." Again and again, then, the electrode tip was applied to this point. Each time, she heard an orchestra playing the same piece of music. She was asked to describe the music. When the electrode was applied again, she began to hum a tune, and all in the operating room listened in astonished silence.

Neurosurgeon Wilder Penfield (1891 – 1976) – Brain stimulation could evoke complex perceptions as well.
During this postoperative evaluation, the patient's face expressed profound sadness within five seconds after a current was delivered. Although still alert, the patient leaned to the right, started to cry, and verbally communicated feelings of sadness, guilt, uselessness, and hopelessness such as “I'm falling down in my head, I no longer wish to live, to see anything, hear anything, feel anything. . .” Her depression disappeared less than 90 seconds after stimulation was stopped.
Big Question 2: Can Brain Stimulation Be Used to Treat Complex Neuropsychiatric Disorders (e.g. Depression)?
All patients spontaneously reported acute effects including “sudden calmness or lightness,” “disappearance of the void,” sense of heightened awareness, increased interest, “connectedness,”.
Brain Stimulation 101 - Clinical

Clinical Trial Targets
Deep Brain Stimulation for Depression

Molecular Psychiatry (2018) 23, 1094-1112; doi:10.1038/mp.2018.2
Brain Stimulation 101 - Clinical

Closed-loop neuromodulation in an individual with treatment-resistant depression

Katherine W. Scangos, Ankit N. Khambhati, Patrick M. Daly, Ghassan S. Makhoul, Leo P. Sugrue, Hashem Zamanian, Tony X. Liu, Vikram R. Rao, Kristin K. Sellers, Heather E. Dawes, Philip A. Starr, Andrew D. Krystal & Edward F. Chang
Big Question 3: What if you don’t want electrodes permanently implanted in your brain?
Brain Stimulation 101 - Clinical

Transcranial Magnetic Stimulation is a method for non-invasively affecting the electric activity of the brain (Depth ~ 2-4 cm)
Brain Stimulation 101 - Clinical

Rapidly Alternating Magnetic Fields Can Create an Electric Current Strong Enough to Directly Activate Neurons in the Brain!
Brain Stimulation 101

Motor Mapping is Discrete Enough to Evoke Movements in Single Digits (Like Penfield!)
Brain Stimulation 101 - History

First Demonstration of TMS was in 1985 (Tony Barker)
Brain Stimulation 101 - Theory

Clinical Trial Targets For Deep Brain Stimulation for Depression Are Very Deep

Molecular Psychiatry (2018) 23
1094-1112

rTMS is Superficial!...so how could it work?
Brain Stimulation 101 - Theory

Superficial Brain Regions Can Regulate Deeper “Depression” Related Circuits (Sub-Genual Cingulate)

rTMS – stim site.

Sub-Genual Cingulate Connectivity Pattern

Fox et. al., PNAS, 2016
Brain Stimulation 101 - Theory

Repeated Daily rTMS Treatment Can Drive Long-Term Changes in Depression—Related Circuits

Downar and Daskalakis, Brain Stimulation 2013.
TMS can be targeted to abnormal networks
Brain Stimulation 101 – Clinical

First Trials of rTMS for Depression were in the mid-1990s - Repetitive Patterns of rTMS were Used Daily to Increase Activity to Dorsolateral Prefrontal Cortex.
**Brain Stimulation 101 – Clinical**

Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial

Daniel M Blumberger, Fidel Vila-Rodriguez, Kevin E Thorpe, Kfir Feffer, Yoshihiro Noda, Peter Giacobbe, Yuliya Knyazhnytska, Sidney H Kennedy, Raymond W Lam, Zafiris J Daskalakis, Jonathan Downar

- **Lancet:** One of largest studies of effects of rTMS (response rate of 49%, remission rate of 32%).

- First study to show a “3” minute TMS protocol (“theta burst”) is as effective as longer protocols (~37.5 mins) - changed practice of rTMS treatments.
Brain Stimulation 101 – Clinical

Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial

Daniel M Blumberger, Fidel Vila-Rodriguez, Kevin E Thorpe, Kfir Feffer, Yoshihiro Noda, Peter Giacobbe, Yuliya Knyazhynska, Sidney H Kennedy, Raymond W Lam, Zafiris J Deskalakis, Jonathan Downar

- Common side effects (see left)
- Risks:
  - 1/30,000 seizure risk/treatment.
  - Exacerbation of illness
  - Trigerring of a manic episode (all similar to risks observed with other antidepressant treatments.)

<table>
<thead>
<tr>
<th>Number of participants reporting each adverse event (%)</th>
<th>10 Hz rTMS group (n=204)</th>
<th>iTBS group (n=208)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>131 (64%)</td>
<td>136 (65%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (11%)</td>
<td>14 (7%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (4%)</td>
<td>18 (9%)</td>
</tr>
<tr>
<td>Unrelated medical problem†</td>
<td>47 (23%)</td>
<td>46 (22%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (7%)</td>
<td>16 (8%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14 (7%)</td>
<td>10 (5%)</td>
</tr>
<tr>
<td>Anxiety or agitation</td>
<td>8 (4%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Back or neck pain</td>
<td>7 (3%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Unrelated accidents</td>
<td>2 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>1 (&lt;1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Migraine aura</td>
<td>3 (1%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Abnormal sensations</td>
<td>2 (1%)</td>
<td>4 (2%)</td>
</tr>
</tbody>
</table>

rTMS = repetitive transcranial magnetic stimulation. iTBS = intermittent theta burst stimulation. †p>0.05 on Fisher’s exact tests for each pair of proportions. †Predominantly common infections such as colds and flus.

Table 3: Adverse events
TMS – Current and Future Research

25 years later...lots of questions have been answered (many by Dr. Jeff Daskalakis). Many interesting research questions remain (various clinical trials on-going at UCSD And other places related to the below questions).

- Where to Stimulate (lots of potential targets for various disorders)?
- How to stimulate (patterns of stimulation which are optimal to treat depression).
- Personalized brain-based (MRI / EEG) based stimulation protocols
- Combine rTMS with psychotherapy, meditation or other behavioral/life-style practices.

Brain Stimulation 101 - Future

Medi-rTMS Trial (2-site, UCSD/SDVA Medical Center)

Combine rTMS with Novel Cognitive/Behavioral Strategies to Activate the Brain / Mind at the Same Time