Medial and Lateral Prefrontal Cortex Neuromodulation Therapies in Depression: A Continuum
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disclosures
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Medical University of South Carolina
1997-2011
depression is primarily a subjective experience.
diminishing returns with Rx: STAR*D

a gravitational pole
Brain Stimulation: The Paradigm Shift

- Electroconvulsive therapy (ECT) FDA APPROVED
- Magnetic seizure therapy (MST)
- Focal electrically-administered seizure therapy (FEAST)
- Transcranial Direct Current Stimulation (tDCS)
- Transcranial Alternative Current Stimulation (tACS)
- Transcranial magnetic stimulation (TMS) FDA APPROVED 2008
- Vagus nerve stimulation (VNS) FDA APPROVED 2005
- Deep brain stimulation (DBS) HDE FDA APPROVED OCD 2009
- Epidural prefrontal cortical stimulation (EpCS)
- Responsive Neurostimulation (RNS)

Brain stimulation tools for depression

<table>
<thead>
<tr>
<th>Technique</th>
<th>Convulsive?</th>
<th>Site</th>
<th>MDE evidence</th>
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<tbody>
<tr>
<td>ECT</td>
<td>C</td>
<td>Cortical</td>
<td>+ RCT</td>
</tr>
<tr>
<td>rTMS</td>
<td>C</td>
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<td>+ RCT</td>
</tr>
<tr>
<td>MST</td>
<td>C</td>
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<td>Open Series</td>
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<tr>
<td>tDCS</td>
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<tr>
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<td>EPI-IMRI</td>
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<tr>
<td>FEAST</td>
<td>C</td>
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</table>
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Accessing the network(s)

Frontal pole (BA10)
Higher level mnemonic control operations
Control of emotion, memory and motivation

Middle frontal gyrus (BA9/46)
Organization, monitoring and verification of information
Integration of cognition and emotion to control thought and behavior

Critical regions in the experience of self

vmPFC Functional Connectivity in Depression
REMT: Depressed show more ventral activation (red) compared to matched controls (blue).

MDD versus Controls

Chahine et al, 201 in preparation

Occipital Alpha Rhythm EEG fMRI

Something is missing
The brain is a Self-Organizing Non-Stationary System

Complexity shape the floor upon which the activity takes place

Figure 1: Possible scenarios of the system moving to a pathological attractor state due to a therapeutic external impact: A: rampant of the system, B: pathological to non-pathological transition, C: escape from the pathological state. D: initiation of the pathological state, E: initiation resulting for the exit from the pathological state.
Taleb [increase play generates opportunities]  
Mandell [intermittency]  
and/or Freeman [intensity]

Diminished complexity with anesthesia

Diminished complexity with depression
Hypothesis:
Changing the landscape, will increase strange attractors and can treat depression by shortening episode or increasing mental flexibility.

Accessing the network(s)

How to get from A to B?

Manji, Drevets, Charney, Nature Medicine 2001
Mayberg et al 1999
How to get from A to B?

WHERE you stimulate
HOW you stimulate,
WHEN you stimulate,

& WHAT is the underlying functional activity of brain region at time of stimulation

….. will determine how far can you reach transynaptically to modulate the network

N= 23 unmedicated depressed individuals
FSL; random effects whole brain analysis. .
All clusters corrected for multiple comparisons with p<0.05 and z>2.3 cluster forming threshold

Left PFC TMS fmRI in depression
TMS optimal targeting

NIMH R01 MH62154

Antidepressant relationship to placement:
\[ R^2=0.294, \text{ d.f.}=2, F=5.20, p = 0.013 \]
\[ X (\beta=-0.022; p=0.019); Y (\beta=0.012; p=0.057) \]

Herbsman et al Biol Psych 2009

TMS optimal targeting by visual inspection and coil position adjustment

Johnson et al Biol Psych 2013

DBS optimal targeting

Riva Posse et al 2014
DBS to AMN Thalamus (not VLN) leads to neurogenesis in the hippocampus

Shamma et al, Brain Stimulation 2015

How to get from A to B?

**HOW** you stimulate

Relation of coil orientation and underlying white matter fibers

R21- MH065630-01A1

(Herbison et al, Human Brain Mapping 2009)
Over 75% of the variance of MT is explained by SCD and fiber orientation.

Cortical Spinal Track:
\[ R^2 = 0.824, F = 20.3, p = 0.001 \]
[SCD (p = 0.001) & PIC PDD-Y (p = 0.008)].

Hand Knob:
\[ R^2 = 0.767, F = 14.3, p = 0.001 \]
[SCD (p = 0.001) but not HK PPD-Y (p = 0.058)].

The illustration was modified by permission from Ruohonen et al. 2002.

Relationship between MT, SCD and Orientation of white fiber tracks.

TMS' parameters of stimulation.

Transcranial Magnetic Stimulation SPECT.
Vagus Nerve Stimulation fMRI

Matrix
Decreases with Time
Increases with HDRS

Nahas, 2007 Neuropsychopharmacology
(Z>2.45)

Right Insula and Middle Prefrontal Cortex relationship to antidepressant response and time

Increase of BDNF in hippocampus after DBS for 7 days

Nahas et al 2009
WHEN you stimulate, & WHAT is the underlying functional activity of brain region at time of stimulation

.... will determine how far can you reach transynaptically to modulate the network

Left PFC single session rTMS in post-operative pain

Borckardt et al Pain 2011

Active state interaction

Fox et al In preparation
Enhanced functional connectivity with Lamotrigine. Role of adjunctive pharmacology?

24h DBS to infra-limbic w & w/o desipramine

**HOW** you stimulate,  
**WHERE** you stimulate,  
& **WHAT** is functional activity of underlying activity

….. will determine how far can you reach transynaptically to modulate the network

And

Determine your side effects!
DBS at STN (or SN) Causes Acute Depression

Separate Benefits / Risks

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Brain stimulation tools


Won Hee Lee et al 2012
FEAST SPECT

Chahine et al 2014 Brain Stim 2014

FEAST 64-channel EEG

Interhemispheric coherence arcs with lead values in right hemisphere
Decreased right frontal drive with reversed electrodes placement

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Brain stimulation tools

Bilateral Epidural Prefrontal Cortical Stimulation for TRD
cognition, executive control and integration of emotion: 2 complimentary networks

NARSAD+Medtronic+GCRC+Neurosurgery+Anesthesia+CAIR+BSL

NIMH Mood Chart: 30-year span
In the last 12 years

VNS

Mood Stabilizers

1996 2001 2008

Antidepressants

Real-time identification of target

Nahas et al 2010

Direct connections to amygdala and subgenual cingulate
intra-operative testing

These subjective changes with parametric modulation become more subtle over time.

emotional appraisal

Hajcak et al 2011

BA 46 stimulation down-regulates LPP
medial stimulation (BA 10) affects mentalizing

Intermittency – random transitivity paradigm

<table>
<thead>
<tr>
<th>Time</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
<th>Subject 5</th>
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<td>1</td>
<td>38</td>
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</tr>
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</table>

Nahas et al 2010
Williams et al 2016

objective improvement over time
Change is course of illness? Big clinical picture

Closed loop feedback

Increasing play will generate opportunities
Currently looking
- Post-doc
- Neuromodulation Medicine Fellowship

Email me:
znahas@umn.edu

Thank you
Interventional Psychiatry Program
Treatment Resistant Depression Program