Noninvasive Neuromodulation Applications

Sarah H. Lisanby, MD

Director, Translational Research Division
Chief, Noninvasive Neuromodulation Unit
Experimental Therapeutics & Pathophysiology Branch
NIMH

Co-Lead Team B: BRAIN Initiative - NIH

7/13/2016
The Promise: NeuroMod for Therapeutics

- Complementary to Neuropharm and Psychosocial Interventions
- 3rd pillar of modern clinical practice
- Promise to turn knowledge of circuitry into therapeutic targets
The Promise: NeuroMod for Therapeutics

- Complementary to Neuropharm and Psychosocial Interventions
- 3rd pillar of modern clinical practice
- Promise to turn knowledge of circuitry into therapeutic targets

Tang, Posner, Rothbart, Volkow. 2015
Clinical NeuroMod: Current State of the Art

- Clinically effective, FDA-approved treatments
Clinical NeuroMod: Current State of the Art

• Clinically effective, FDA-approved treatments

• Unparalleled efficacy

Source: STAR-D Trial
Clinical NeuroMod: Current State of the Art

- Clinically effective, FDA-approved treatments
- Unparalleled efficacy
- Rapidly resolves suicide risk

Clinical NeuroMod: 
Current State of the Art

• Clinically effective, FDA-approved treatments

• Less invasive alternatives now on the market
Clinical NeuroMod: Current State of the Art

- Clinically effective, FDA-approved treatments
- Less invasive alternatives now on the market
- New devices in various stages of development
Clinical NeuroMod: Current State of the Art

• Clinically effective, FDA-approved treatments
• Safe, noninvasive brain-behavior mapping tools
  – Image-guided, stereotaxic stimulation
  – Precisely temporally coupled with cognitive/behavioral task performance
Clinical NeuroMod: 
Current State of the Art

- Clinically effective, FDA-approved treatments
- Safe, noninvasive brain-behavior mapping tools
  - Image-guided, stereotaxic stimulation
  - Precisely temporally coupled with cognitive/behavioral task performance
  - Simultaneous physiological readout – fMRI, ERP

TMS/fMRI Interleaving
Clinical NeuroMod: Current State of the Art

- Clinically effective, FDA-approved treatments
- Safe, noninvasive brain-behavior mapping tools
  - Image-guided, stereotaxic stimulation
  - Precisely temporally coupled with cognitive/behavioral task performance
  - Simultaneous physiological readout – fMRI, ERP
Clinical NeuroMod: Current State of the Art

- Clinically effective, FDA-approved treatments
- Safe, noninvasive brain-behavior mapping tools
- Affordable, portable technologies on the horizon with excellent safety profiles
  - tDCS
  - tACS

2-electrode config
Multi-electrode config
Clinical NeuroMod:
Current State of the Art

- Clinically effective, FDA-approved treatments
- Safe, noninvasive brain-behavior mapping tools
- Affordable, portable technologies on the horizon with excellent safety profiles
Clinical NeuroMod: Current State of the Art

- Clinically effective, FDA-approved treatments
- Safe, noninvasive brain-behavior mapping tools
- Affordable, portable technologies on the horizon with excellent safety profiles
- Growing industry base, supported by FDA approvals and insurance reimbursement in many regions
Clinical NeuroMod: Current State of the Art

- Clinically effective, FDA-approved treatments
- Safe, noninvasive brain-behavior mapping tools
- Affordable, portable technologies on the horizon with excellent safety profiles
- Growing industry base, supported by FDA approvals and insurance reimbursement in many regions
- Strong consumer uptake and growing demand
Clinical NeuroMod: Current State of the Art

- Clinically effective, FDA-approved treatments
- Safe, noninvasive brain-behavior mapping tools
- Affordable, portable technologies on the horizon with excellent safety profiles
- Growing industry base, supported by FDA approvals and insurance reimbursements
- Strong consumer uptake and growing demand
- Do-It-Yourself (DIY) community, and life-style companies entering the picture

So What’s Wrong with this Picture?
ECT highly effective, but arguably under utilized

TMS safer alternative, but efficacy presently falls short of ECT, and is comparable to available pharmacotherapy

2 major DBS-depression trials failed despite early promise

Why?

O’Reardon et al. Biol Psychiatry 2007
Limitations of Current NeuroMod Impacting Efficacy

- Variable practice, with variable results
- Lack of knowledge of optimal dosing
- Limited knowledge of mechanisms of action at a cellular and circuit level to inform dosing strategies

Black Box Approach to Neuromod

- Mechanism of action
- Duration of action
- Optimal dosing
- Target engagement
Key Research Opportunities

• Determine fundamental dose/response relationships employing expertise and equipment uniquely poised to address these questions, such as
  – NHP
  – Clinical populations intensively studied in the CC
  – MEG, Receptor PET
  – TMS/fMRI interleaving

• Collaborative studies across disciplines, esp. engineering

• Leverage depth of expertise in the physiological effects of noninvasive neuromod in neurological applications to address relatively less explored complex neurobehavioral conditions in psychiatry

• Innovate novel tools, informed by E-field modeling
Key Research Considerations

• Don’t treat neuromod tools as off-the-shelf black boxes

• Innovate novel paradigms for
  – Stimulation
  – Analysis / signal processing
  – Perturbation/imaging

• Pay attention to precision in dosing – space/time/context
3 Dimensions of Dosing for NextGen NeuroMod

Space

Spiral Galaxy M83
Credit: NASA, ESA, and the Hubble Heritage Team
3 Dimensions of Dosing for NextGen NeuroMod

Space

Spiral Galaxy M83
Credit: NASA, ESA, and the Hubble Heritage Team

Time

The Persistence of Memory – Salvador Dali

Context

“Never, ever, think outside the box.”
3 Dimensions of Dosing for NextGen NeuroMod

Space

Spiral Galaxy M83
Credit: NASA, ESA, and the Hubble Heritage Team

Time

The Persistence of Memory – Slavador Dali

Context


3 Dimensions of Dosing for NextGen NeuroMod

Where

Spiral Galaxy M83
Credit: NASA, ESA, and the Hubble Heritage Team

When

The Persistence of Memory – Slavador Dali

How
Advice

- Don’t treat neuromod tools as off-the-shelf black boxes
- Innovate novel paradigms for
  - Stimulation
  - Analysis / signal processing
  - Perturbation/imaging
- Pay attention to precision in dosing – space/time/context
- Target distributed networks (circuits), not discrete locations under the coil (coordinates)
Transsynaptic action of TMS

- TMS/fMRI interleaving paradigm
- Distal activations and deactivations induced by single pulse TMS to frontal cortex

Luber et al. In Submission
Advice

• Don’t treat neuromod tools as off-the-shelf black boxes
• Innovate novel paradigms for
  – Stimulation
  – Analysis / signal processing
  – Perturbation/imaging
• Pay attention to precision in dosing – space/time/context
• Target distributed networks (circuits), not discrete locations under the coil (coordinates)
• Employ E-field modeling coupled with connectivity mapping to know where you stimulated
An integrated framework for targeting functional networks via transcranial magnetic stimulation

Alexander Opitz\textsuperscript{a,b,*}, Michael D. Fox\textsuperscript{c,d,e}, R. Cameron Craddock\textsuperscript{a,b}, Stan Colcombe\textsuperscript{a}, Michael P. Milham\textsuperscript{a,b,*}

Realistic E-Field Modeling

Human Connectome Network Identification

NeuroImage 127 (2016) 86–96
Impact of Coil Orientation
Connectivity of TMS Depression Targets

DLPFC Regions from Fox et al. 2012

<table>
<thead>
<tr>
<th>Study/Site</th>
<th>Average 5 cm Coordinates</th>
<th>-41</th>
<th>18</th>
<th>49</th>
<th>-41</th>
<th>16</th>
<th>54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbsman et al 2009 Responders</td>
<td></td>
<td>-46</td>
<td>25</td>
<td>44</td>
<td>-46</td>
<td>23</td>
<td>49</td>
</tr>
<tr>
<td>Herbsman et al 2009 Nonresponders</td>
<td></td>
<td>-41</td>
<td>19</td>
<td>50</td>
<td>-41</td>
<td>17</td>
<td>55</td>
</tr>
<tr>
<td>Herwig et al 2003 EEG (F3) Site</td>
<td></td>
<td>-37</td>
<td>27</td>
<td>44</td>
<td>-37</td>
<td>26</td>
<td>49</td>
</tr>
<tr>
<td>Rajkowska and Goldman-Rakic 1995 BA46 Definition</td>
<td></td>
<td>-44</td>
<td>40</td>
<td>25</td>
<td>-44</td>
<td>40</td>
<td>29</td>
</tr>
<tr>
<td>Rajkowska and Goldman-Rakic 1995 BA9 Definition</td>
<td></td>
<td>-36</td>
<td>40</td>
<td>38</td>
<td>-36</td>
<td>39</td>
<td>43</td>
</tr>
<tr>
<td>Paus et al 2001 TMS Target</td>
<td></td>
<td>-40</td>
<td>32</td>
<td>30</td>
<td>-40</td>
<td>31</td>
<td>34</td>
</tr>
<tr>
<td>Fitzgerald et al 2009 TMS Target</td>
<td></td>
<td>-46</td>
<td>45</td>
<td>35</td>
<td>-46</td>
<td>45</td>
<td>38</td>
</tr>
<tr>
<td>Rusjan et al 2010 TMS Target</td>
<td></td>
<td>-50</td>
<td>31</td>
<td>32</td>
<td>-50</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>Fox et al 2012 optimal TMS Target</td>
<td></td>
<td>-38</td>
<td>44</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fox et al 2012 peak TMS Target</td>
<td></td>
<td>-44</td>
<td>38</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NeuroImage 127 (2016) 86–96
Advice

• Don’t treat neuromod tools as off-the-shelf black boxes
• Innovate novel paradigms for
  – Stimulation
  – Analysis / signal processing
  – Perturbation/imaging
• Pay attention to precision in dosing – space/time/context
• Target distributed networks (circuits), not discrete locations under the coil (coordinates)
• Employ E-field modeling coupled with connectivity mapping to know where you stimulated
• Employ measures of target engagement (TMS/fMRI, TMS/EEG) to demonstrate target engagement and be able to interpret results (both successes and failures)
Target Engagement – Working Memory

- Domain of Function – Working Memory

Stimulus (3 s)
Retention (7 s)
Probe (3 s)
ITI (5.5 s)

Sternberg Delayed-Match-to-sample task

K S Z
+ R M C

All Rights Reserved, Duke Medicine 2007
Target Engagement – *Working Memory*

- **Domain of Function** – *Working Memory*
- **Target** – *Neural Reserve & Compensation Circuit*
Target Engagement – *Working Memory*

- Domain of Function – *Working Memory*
- Target – *Neural Reserve & Compensation Circuit*
- Intervention – *TMS + WM-training*
  - TMS Neuronavigated to WM-resilience network
  - Simultaneous WM-Training + TMS paired delivery paradigm

fMRI-Guided TMS

Working Memory Training

Simultaneous
Target Engagement – Working Memory

- Domain of Function – Working Memory
- Target – Neural Reserve & Compensation Circuit
- Intervention – TMS + WM-training
- Demonstration of target engagement – Compensation Circuit expression
  - Predicted shift in fMRI network expression during WM task performance
Target Engagement – Working Memory

• Domain of Function – *Working Memory*
• Target – *Neural Reserve & Compensation Circuit*
• Intervention – *TMS + WM-training*
• Demonstration of target engagement – *Compensation Circuit expression*
  – Predicted shift in fMRI network expression during WM task performance
• Translational trajectory strategy
A Translational Trajectory for Targeted Intervention Development

- Prevent experimentally induced deficit
- Enhance Resilience to illness-related deficit
- Remediate clinical symptoms
- Promote Resilience to experimentally induced deficit
- Remediate experimentally induced deficit

Healthy volunteer

Clinical Samples

Enhance Normal Function

Restore Healthy Function
A Translational Trajectory for Targeted Intervention Development

Enhance Normal Function

Remediate experimentally induced deficit

Prevent experimentally induced deficit

Promote Resilience to experimentally induced deficit

Luber et al Brain Research 2007;1128:120-129

Remediate clinical symptoms

Enhance Resilience to illness-related deficit

- Healthy volunteers
- rTMS+WM training enhanced WM performance in site/frequency dependent fashion

Restore Healthy Function
A Translational Trajectory for Targeted Intervention Development

Remediate experimentally induced deficit

Enhance Resilience to illness-related deficit


Promote Resilience to experimentally induced deficit

• Targeted circuit associated with resilience to sleep deprivation

Remediate clinical symptoms

• rTMS+WM training remediated WM deficit after 2 full days of sleep deprivation

Enhance Normal Function

Restore Healthy Function
A Translational Trajectory for Targeted Intervention Development

- Prevent experimentally induced deficit
- Remediate experimentally induced deficit
- Enhance Resilience to illness-related deficit
- Promote Resilience to experimentally induced deficit
- Enhance Normal Function
- Remediate clinical symptoms

Degree of improvement correlated with network expression


$r = -0.58, p < 0.025$
A Translational Trajectory for Targeted Intervention Development

- Prevent experimentally induced deficit
- Remediate experimentally induced deficit
- Enhance Resilience to illness-related deficit
- RemEDIATE clinical symptoms
- Promote Resilience to experimentally induced deficit
- Enhance Normal Function
- Restore Healthy Function

• RCT of TMS+Task to resilience target (2/day x 2 days)
  - Prevented memory decrement and memory lapses a full 18 hrs after the last TMS

Luber et al. Sleep 2013; 36:857-71
A Translational Trajectory for Targeted Intervention Development

- Prevent experimentally induced deficit
- Remediate experimentally induced deficit
- Enhance Resilience to illness-related deficit
- Promote Resilience to experimentally induced deficit
- Remediate clinical symptoms
- Enhance Normal Function
- Healthy volunteer
- Clinical Samples
- Restore Healthy Function
A Translational Trajectory for Targeted Intervention Development

- Prevent experimentally induced deficit
- Enhance Resilience to ILLNESS-related deficit
- Promote Resilience to experimentally induced deficit
- Remediate clinical symptoms
- Remediate experimentally induced deficit
- Enhance Normal Function
- Restore Healthy Function

Healthy volunteer

Clinical Samples
A Translational Trajectory for Targeted Intervention Development

Remediate experimentally induced deficit

Prevent experimentally induced deficit

Enhance Resilience to AGE-related deficit

Remediate clinical symptoms

Healthy volunteer

Clinical Samples

Enhance Normal Function

Restore Healthy Function

Promote Resilience to experimentally induced deficit
A Translational Trajectory for Targeted Intervention Development

Prevent experimentally induced deficit

Remediate experimentally induced deficit

Enhance Resilience to AGE-related deficit

Promote Resilience to experimentally induced deficit

Remediate clinical symptoms

Enhance Normal Function

Restore Healthy Function

Targeting neural compensation network enhanced WM selectively in elderly

Luber et al in prep

*p<0.05; n=21
A Translational Trajectory for Targeted Intervention Development

Enhance Normal Function

Remediate experimentally induced deficit

Prevent experimentally induced deficit

Promote Resilience to experimentally induced deficit

Enhance Resilience to AGE-related deficit

Remediate clinical symptoms

Next Steps – MCI, Dementia, and WM impairment in trans-diagnostic samples, including addictions

Restore Healthy Function
The Delayed Match-to-Sample Task (Sternberg Variant)

Blank (3 sec)  
Stimulus (3 sec)  
Retention (7 sec)  
Probe (3 sec)

Either Set-Size 1

TMS here

Either a True Positive

Or a True Negative

Time in Trial
Dose Finding to Select Optimal TMS Paradigm in Space / Time / Context

- TMS during task performance to promote network utilization and enhance performance.
- Sham-controlled randomized trial, between subject
Frequency-Dependent Effects of rTMS During WM Task Performance

- 5 Hz TMS to precuneus during retention phase reduced RT by 50 ms (p<0.002)
- Effect specific to precuneus - not seen with TMS at dorsolateral prefrontal cortex

Luber et al Brain Research 2007;1128:120-129
Phase-Frequency Interaction

- Replication, in an independent sample, of 5 Hz retention phase improvement
- Probe phase 20 Hz worsened performance

Luber et al. Brain Research 2007;1128:120-129
TMS + Simultaneous Working Memory Training Remediates Cognitive Performance

- Frequency- and site-specific working memory enhancement with 5 Hz TMS to precuneus
- Site-specific cognitive enhancement with 5 Hz TMS to sleep deprivation resilience network

Luber et al. Cerebral Cortex 2008;18:2077

Luber et al. Brain Research 2007;1128:120-129
**TMS + Simultaneous Working Memory Training Prevents Cognitive Deficits**

- RCT of TMS+Task to resilience target (2/day x 2 days)
- Prevented memory decrement and memory lapses a full 18 hrs after the last TMS
- Change in fMRI network localized under TMS coil

---

Luber et al Sleep 2013;36:857-71
Key Methodological Decisions

- Spatial aspects of dosing
  - Coil design, position, orientation
- Temporal aspects of dosing
  - Pulse shape, train parameters
- Contextual aspects of dosing
  - Concurrent task performance to engage network
- Sham / Comparison condition
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.
Meet the NNU Team

Lisanby

Luber

Radman

Deng

Martinez-Kaigi

Experimental Therapeutics & Pathophysiology Branch

Park, Staff of 7SE

Zarate

Noh, van Gelderen, Asturias
Any Questions?