Noninvasive Neuromodulation
Current State & Future Directions

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Noninvasive Neuromodulation

Electro-convulsive Therapy
**Neuromodulation Tools**

- **Magnetic**
  - Transcranial Magnetic Stimulation (TMS)
  - Magnetic Seizure Therapy (MST)

- **Implanted**
  - Vagus Nerve Stimulation (VNS)
  - Deep Brain Stimulation (DBS)

- **Electrical**
  - Transcranial Direct Current Stimulation (TDCS)
  - Electro-convulsive Therapy (ECT)
Noninvasive Neuromodulation
Application of energy through the scalp and skull to change brain function
Noninvasive Neuromodulation

- Why do we need it?
- What is the current state of the science and practice?
- What’s next?
Suicide Rates Climbing

Source: Centers for Disease Control

Figure 1. Age-adjusted suicide rates for females, by race and Hispanic origin: United States, 1999 and 2014

Figure 2. Age-adjusted suicide rates for males, by race and Hispanic origin: United States, 1999 and 2014

* Difference in rates between 1999 and 2014 was significant (p < 0.05).

NOTES: Suicide is identified with ICD-10 codes X60-X84, and Y87.0. Death rates for non-Hispanic American Indian or Alaska Native (AIAN), non-Hispanic Asian or Pacific Islander (API), and Hispanic persons may be underestimated and should be interpreted with caution; see Data source and methods. SOURCE: CDC/NCHS, National Vital Statistics System mortality data, 1999 and 2014, available from: CDC WONDER online database.
Mental Disorders are Chronic and Disabling

Source: WHO 2008

Behavioral contributions to poor medical outcomes:
Depression, stress, diet, exercise, smoking, treatment compliance

The single best way to improve overall health is to improve brain health

Limited Efficacy of Pharmacotherapy

Source: STAR-D Trial

- Highlights need for more effective approaches
- Diminishing returns from trying additional medications
Noninvasive Neuromodulation

• Why do we need it?
• What is the current state of the science and practice?
• What’s next?
The ability to change brain function noninvasively has been a paradigm shift for neuroscience research.
Current State of Neuromod in Practice

Neuro-modulation Therapy

Psychotherapy

Paradigm Shift for Clinical Care

Pharmacotherapy
Current State of Neuromod in Practice

- Highly effective, FDA-cleared treatments

ECT Treatment Visit

Percent of Patients

ECT

Electroconvulsive Therapy
Current State of Neuromod in Practice

- Highly effective, FDA-cleared treatments
- Less invasive alternatives now available, with more in development
- Focal stimulation enables translation of circuitry underlying disorders into targeted treatment
Circuit-Guided Treatment

Clinical TMS, FDA Approved for Depression, 2008

dTMS: FDA approved Jan 2013

Prefrontal cortex

Hypothalamus

Area 25

Amygdala

DBS

Humanitarian Device Exemption for Obsessive Compulsive Disorder, 2009

National Institute of Mental Health
Current State of Neuromod in Practice

- Off-label use a reality today
- Home use a reality

**tDCS**

Transcranial Direct Current Stimulation (tDCS) is a safe, new, non-invasive procedure which provides relief for treatment-resistant neurologic, psychiatric and chronic pain conditions. tDCS also improves attention, memory and learning for both healthy individuals and patients with disabilities. tDCS is performed at the clinic in Atlanta or it can be self-administered with training and supervision through the Home-Use Program.

Source: website advertising a brain stimulation clinic
US athletes using brain stimulation to improve Olympic performance

Published time: 7 Aug, 2016 10:33
Edited time: 7 Aug, 2016 10:42
Current State of Neuromod - Recreation

- Sports
- Gaming
- Attention enhancement
- Lucid dreaming
- Other claims
Clinical State of the Art of Clinical NeuroMod Dosing

- FDA cleared TMS devices, with the same clinical indication, differ radically in:
  - spatial distribution
  - temporal parameters

Deng, Peterchev and Lisanby, 2008

Coil

- 10 Hz
- 4 sec
- ITI=26s
- 3000 pulses/session

E field

- 18 Hz
- 2 sec
- ITI=20s
- 1980 pulses/session

Figure 8

H-Coil
Optimal dosing unknown, infinite parameter space

- Spatial targeting – where to put it
- Temporal targeting – how to tune it
- Controlling context – state of brain at time of stim

Interactions of all of the above

Delivered Dose

E-field distribution

Frequency, train duration, pulse shape

Context of Use

Endogenous & task-related activity, oscillatory phase, sleep/wake cycle, meds, social context
Neuromod Technique – Evolving

- Optimizing delivered dose
  - *Multi-focal targeting* to sculpt connectivity
  - E.g. paired associative stimulation via Hebbian plasticity

Delivered Dose

Context of Use

Endogenous activity, task-related activity, oscillatory phase, concomitant meds, social context

E-field distribution
Frequency, train duration, pulse shape
Neuromod Technique – Evolving

- Optimizing delivered dose
- Optimize dose-context interaction

- *Multi-modal targeting*: Cognitive Paired Associative Stimulation (C-PAS): Stimulation time-locked to cognitive task performance

Delivered Dose

Context of Use

- Endogenous activity, task-related activity, oscillatory phase, concomitant meds, social context

E-field distribution

Frequency, train duration, pulse shape
Optimizing delivered dose
Optimize dose-context interaction

- **Multi-modal targeting**: Cognitive Paired Associative Stimulation (C-PAS): Stimulation time-locked to cognitive task performance

Delivered Dose | Context of Use
---|---
fMRI-Guided TMS | Working Memory Training
Optimizing delivered dose
Optimize dose-context interaction

- **Multi-modal targeting**: Cognitive Paired Associative Stimulation (C-PAS): Stimulation time-linked to cognitive task performance

Research Report

**Facilitation of performance in a working memory task with rTMS stimulation**

Remediation of sleep-deprivation induced working memory impairment with fMRI-guided TMS: Testing the role of resilience-associated cortical networks

B. Luber, A. Stanford, A.D. Bulow, P. Nguyen, T. Politi, B.C.


Bruce Luber, PhD; Jason Steffen, PhD; Adrienne Tucker, PhD; Christian Habeck, PhD; Angel V. Peterchev, PhD; Zhi-De Deng, MEng; Robert C. Basner, MD; Yaakov Stern, PhD; Sarah H. Lisanby, MD
Noninvasive Neuromodulation

• Why do we need it?
• What is the current state of the science and practice?
• What’s next?
NextGen Tools

THE BRAIN INITIATIVE®

• **Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative**

• **Goal:** to revolutionize our understanding of the human brain by accelerating the development and application of innovative technologies

Source: Human Connectome Project

Next-gen tools to probe neural control of thoughts, feelings, movements

Brainbow transgenes. Credit: Joshua Sanes, Ph.D., Harvard

[Image of brain map, NextGen tool, and Brainbow transgene]
• Noninvasive NeuroMod Tool Development and Optimization
  – RFA-MH-17-245: BRAIN Initiative: Non-Invasive Neuromodulation - **Mechanisms and Dose/Response** Relationships for Targeted CNS Effects (R01)
What’s Next

• Increases in supply
  – Clinics offering noninvasive neuromod treatments
  – Companies offering products direct to consumers
  – Do-It-Yourself community

• Increases in demand
  – From patients seeing care for clinical disorders
  – From consumers seeking neuroenhancement

• Need for
  – Professional guidelines to inform medical practice
  – Guidelines for over-the-counter and consumer products
  – Research to inform dose/response relationships and optimal methods of use to ensure safety and efficacy
TRANSCRANIAL ELECTRICAL STIMULATION: MECHANISMS, TECHNOLOGY AND THERAPEUTIC APPLICATIONS

SEPTMBER 29TH 8:30AM-5:00PM

SEPTMBER 30TH 8:30AM-2:30PM

JOIN US ONLINE! REGISTRATION REQUIRED:
HTTPS://WWW.EVENTBRITE.COM/E/TRANSCRANIAL-ELECTRICAL-STIMULATION-TICKETS-27030688517
Acknowledgements

Noninvasive Neuromodulation Unit (NNU)

Key Collaborators

- Peterchev
- Goetz
- Strauman
- McClintock
- Husain

- R01MH091083 (Pls: Lisanby/Peterchev)
- R01 MH060884 (Pl: Lisanby)
- U01 MH084241 (Pls: Kellner and Lisanby)
- K01 AG031912 (Pl: Luber, Mentor: Lisanby)
- R21 EB00685 (Pls: Lisanby & Peterchev)
- Brain & Behavior Foundation (Lisanby), Stanley Foundation (Lisanby/Husain)

Experimental Therapeutics & Pathophysiology Branch

Park, Martinez-Kaigi, Yu, Staff of 7SE

Zarate
Where is the Federal Funding to Fight Suicide?

In the last 10 years, we’ve invested federal funding to research leading causes of death like HIV/AIDS, heart disease, and prostate cancer. Major progress has led to decreased mortality rates. It’s time we do the same with suicide.

<table>
<thead>
<tr>
<th>Leading Causes of Death</th>
<th>2013 Funding</th>
<th>2003-2013 Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV/AIDS</td>
<td>$2.9 Billion</td>
<td>53.2%</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>$1.2 Billion</td>
<td>29.1%</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>$266 Million</td>
<td>13.7%</td>
</tr>
<tr>
<td>Suicide</td>
<td>$37 Million</td>
<td>20.4%</td>
</tr>
</tbody>
</table>

Death rates taken from Centers for Disease Control data for 2003 and 2013 (most recent available). Each flask represents $1 billion of research funding by the National Institutes of Health.
Leading Risk for Suicide: Mental Illness


Nordentoft et al, JAMA Psychiatry 2011
It's a sad, sad, sad, sad world: Depression and global disability

- Burden borne more by women
- Max in peak working years
- Persists into senior years
# Neuromodulation Toolbox

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>DBS - deep brain stimulation</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Electrical - AC</td>
</tr>
<tr>
<td>ECS - epidural cortical stimulation</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Electrical - AC</td>
</tr>
<tr>
<td>VNS - vagus nerve stimulation</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y**</td>
<td>N</td>
<td>N**</td>
<td>Electrical - AC</td>
</tr>
<tr>
<td>NIR - near infrared light therapy</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Optical</td>
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<tr>
<td>Optogenetic DBS</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Optical</td>
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<tr>
<td>ECT - electroconvulsive therapy</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
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<td>MST - magnetic seizure therapy</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>CES - cranial electrical stimulation</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N*</td>
<td>Electrical - AC</td>
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<tr>
<td>tDCS - transcranial direct current stim.</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N*</td>
<td>N*</td>
<td>N</td>
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<td>LFMS - low field magnetic stimulation</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Magnetic</td>
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<tr>
<td>rTMS - repetitive transcranial mag. stim.</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N*</td>
<td>Y</td>
<td>Y</td>
<td>Magnetic</td>
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<tr>
<td>FUS - focused ultrasound</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>UltraSound</td>
</tr>
</tbody>
</table>

* function of coil type or electrode array, ** limited to vagal afferents
Leading Driver of Disability Worldwide

- Depression is a leading cause of disease burden worldwide

Plot 1: World map showing age-standardised YLD rates (per 100,000) by country
Are we asking the right question?

Depression, Anxiety, Psychosis, Addictions, Traumatic Brain Injury, Autism, Pain, Dementia
Are we asking the right question?

**How does it work?**

- Extracellular Currents
  - Endogenously Generated
  - Exogenously Applied

Emerging role of abnormal neural oscillations in psychiatric disorders
**Neuromod Technique – Evolving**

- Optimal dosing unknown, infinite parameter space
  - Conventional “Dosing dogma” is misleading

<table>
<thead>
<tr>
<th>Technique</th>
<th>Frequency Type</th>
<th>Polarization Type</th>
<th>Effect Type</th>
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</thead>
<tbody>
<tr>
<td>rTMS</td>
<td>High freq</td>
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<td>Excitatory</td>
</tr>
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<td>Continuous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tDCS</td>
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<td>Cathodal</td>
<td>Inhibitory</td>
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<td>TBS</td>
<td>Anodal</td>
<td>Cathodal</td>
</tr>
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</table>

Excitatory & Inhibitory
Electrodes

Higher density, less invasive, longer lasting

CMOS multi-electrode array with >500 contacts
-- Italian Inst. of Technology

Electro-osmotic “self-motile” electrodes
- Stanford U.

Optical Imaging

Deeper, faster, more precise targeting

3-photon imaging of hippocampal neurons >1mm deep in the mouse brain – Cornell (Xu)

Probes

Sensors: voltage, transmitters

Modulators: chemical-genetic, photo-switchable ligands, GPCR signaling

GFP Linked bacterial protein mutated to bind serotonin

New optogenetic serotonin sensor with high SNR in cultured cells – UC Davis (Tian)