Neuromodulation Devices:
The Devil is in the Dosing

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Disclosures

• Off-Label
  – Magnetic Seizure Therapy

• Research Grants
  – NIH, Stanley, Brain & Behavior, NeoSync, Brainsway, NexStim, ANS/St Jude
Major Depression

• A leading cause of disability and suicide

– Affects 121 million people worldwide
– 4th leading contributor to global burden of disease
– By 2020, projected to be 2nd leading cause
– 10 -15% lifetime suicide risk
Major Depression

- A leading cause of disability and suicide
- Often resistant to medications
- Effective alternatives are needed

Source: STAR-D Trial
Electroconvulsive Therapy (ECT)

- Highly Effective in
  - Reducing all cause mortality
  - Inducing remission

Philibert 1995; O’Conner 2001; Kobeissi 2011
Electroconvulsive Therapy (ECT)

- Highly Effective in
  - Reducing all cause mortality
  - Inducing remission
- Prolonging Remission in Depressed Elders (PRIDE)
  - n=222 depressed seniors
  - 82.9% of completers remitted

* Effect of Time: $p<0.001$ from mixed effects model
Electroconvulsive Therapy (ECT)

- Highly Effective in
  - Reducing all cause mortality
  - Inducing remission
  - Rapidly resolving suicidal ideation

0=Absent; 1 life is empty/not worth living; 2 Recurrent thoughts/wishes about death of self; 3=Active suicidal thoughts, threats, gestures; 4=Serious suicide attempt
Electroconvulsive Therapy (ECT)

- Highly Effective in
  - Reducing all cause mortality
  - Inducing remission
  - Rapidly resolving suicidal ideation

- Barriers to use
  - Amnesia risk
Electroconvulsive Therapy (ECT)

- **Highly Effective in**
  - Reducing all cause mortality
  - Inducing remission
  - Rapidly resolving suicidal ideation

- **Barriers to use**
  - Amnesia risk
  - Limited knowledge of optimal dosing strategies

Philibert 1995; O’Conner 2001; Kobeissi 2011
ECT ‘Dose’ Circa 1938

- One size fits all
- Bilateral electrode placement
- Sine wave
- Stimulate until seizure is induced
Early Studies into ECT Dosing

OBSERVATIONS ON MENTAL PATIENTS AFTER ELECTRO-SHOCK

BY HANS LÖWENBACH AND EDWARD J. STAINBROOK

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A generalized convulsion leaves a human being in a state in which all that is called the personality has been extinguished. Although the autonomous functions are operating more or less regularly, the individual does not react for a while to any kind of stimuli and the activity of the cerebral cortex as revealed by the electroencephalogram has almost completely ceased. The convulsions could not be induced which are independent of the stimulus.

Separate shocks were supplemented by studies of 35 other patients undergoing electroconvulsions.

Although we cannot overemphasize the variations in individual responses here relate what we have observed to changes in consciousness from the moment of convulsion to the moment of recovery from unconsciousness.
ECT Dose Matters

- For efficacy

Remission Rate (%)

RUL 1.5 ms PW

Dose above seizure threshold

Sackeim et al. Arch Gen Psychiat 2000
ECT Dose Matters

- For efficacy
- For safety

McCall et al. Arch Gen Psych 2000

Autobiographical memory

Dose above seizure threshold

RUL 1.5 ms PW
Conventional Approach

Rational Approach

In Vivo: Feasibility
- Calibrate to Neural Threshold
- Individualize Pulse Amplitude
- Optimize Train Parameters

Device

Stimulation

Parameters

Ex Vivo: Models
- E-field Distribution

In Vivo: Feasibility

Clinical Trials
- Open Label
- Randomized Trials

Clinically test each stimulation paradigm

Revise stimulation paradigm

Revise

In Vivo: Safety

Animal & Healthy Human Studies
- Cognitive Function
- Tolerability

R01 MH091083; MPI: Lisanby / Peterchev
Defining Dose

- In Space
  - Electrode/coil placement

![Graph showing amnesia score (%)]

Lisanby et al. Arch Gen Psych 2000;57:381
Defining Dose

- In Space
- In Time
  - Pulse shape

Sine Wave

Brief Pulse

Weiner et al 1986
“Effects of stimulus parameters on cognitive side effects”
Defining Dose

- In Space
- In Time
  - Pulse shape

Sackeim et al. Brain Stimulation 2008;1:71-83
Defining Dose

- In Space
- In Time
  - Pulse shape
  - Train parameters
    - Frequency, directionality, duration

Unidirectional

Bidirectional
Spiral Galaxy M83. Credit: NASA, ESA, and the Hubble Heritage Team.
Coil Type Determines Induced Electric Field Spatial Distribution

Round coil

Figure-8 coil
Wide Variety of Coil Designs
Wide Variety of Coil Designs

Wide Variety of E-field Spatial Spread
Coil

E field

Figure-8

H-Coil

Efficacy

Remission Rate (%)

Remission Rate (%)

0

20

40

60

80

100

Active

Sham

Active

Sham

Deng, Peterchev and Lisanby, 2008
Depth/focality/invasiveness trade-off

TMS

Noninvasive
Focal
Not Deep

Noninvasive
Deep
Not Focal

Deep Brain Stimulation

Deep
Focal
Invasive
Can we overcome depth/focality trade-off and achieve noninvasive, focal, deep brain stim?
Noninvasive focal deep brain stimulation

Deep target tracing  DTI ProbTrack  3D rendering
Noninvasive focal deep brain stimulation

Individualized DTI-based Targeting of BA25

TMS/fMRI Interleaving

120% MT – 80% MT contrast; significant cluster (z>2.3, p<.05) in BA25 seed region
Can we make Seizure Therapy safer through E-Field Shaping?
Early Studies into E-field induced by ECT


LEO ALEXANDER, M.D., MAJOR, M.C., A.U.S.
AND
HANS LÖWENBACH, M.D.

- Cat brain
- Current path inferred from congestive-hemorrhagic discoloration of cortex

J Neuropath Exp Neurol 1944; 3:139-171
Realistic Head Modeling of E-Field

Tissue compartments: (a) skin, (b) bone, (c) muscle, (d) sclera, (e) vertebrae, (f) gray matter, (g) lens, (h) orbit, (i) optic nerve, (j) white matter, and (k) spinal cord.

Enables individualized targeting guided by structure and function.
Current Density Distributions

Stimulation Strength Relative to Neural Activation Threshold

Lee et al., EMBC14 submitted
Impact of ECT Electrode Placement on E-field in Brain

Lee et al. Neuroimage 2012
Tetanic Stimulation of Hippocampus by ECT

- Induces and saturates LTP
- Hypothesized role in ECT-induced amnesia

Lee et al., EMBC14 submitted; Stewart & Reid 1993; SteCasarotto et al 2013
E-Field Shaping to Spare Cognition

- Magnetic Seizure Therapy
  - Couples focality of rTMS with efficacy of seizures
  - More focal E field and seizure hypothesized to reduce maladaptive plasticity and spare cognition

More Focal Stimulation with MST vs ECT

Current Density

E field relative to neural activation threshold

ECT

MST

Lee et al. EMBC 2014
More Focal Stimulation with MST vs ECT

- MST stimulates only 4% of total brain volume
- Spares hippocampus from E-field exposure
Unilateral ECT

64 channel current source density analysis of EEG
MST

64 channel current source density analysis of EEG
Randomized Trials on Cognitive Outcomes

RCT of MST vs ECT Cognitive Effects
Moscrip, Terrace, Sackeim, Lisanby. *IJNP 2006*

Safety and Feasibility of MST: Within Subject MST vs ECT
Lisanby, Luber, Schaepfer, Sackeim. *Neuropsychopharm 2003*
MST – 50 Hz
ECT – 6xST, 0.3 ms PW

RCT of HD-MST vs ECT Cognitive Effects
Spellman, McClintock, Terrace, Luber, Husain, Lisanby. *Biol Psychiatry 2008*
Cognitive Sparing with MST

- Rapid reorientation
- Relatively benign neurocognitive profile

Reorientation Time

Verbal Memory

Phonemic Fluency

Complex Problem Solving

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McClintock et al. ACNP 2012

ECT MST
Antidepressant Efficacy of MST*

*100 Hz, vertex

Kayser et al J Psych Research 2011

Lisanby et al In Preparation
Antidepressant Efficacy of MST

HRSD-24

IDS-C

IDS-SR

ECT

MST

Lisanby et al In Preparation
Can we achieve MST-like focality, and safety, with ECT?

• Like ECT with a little “e”
Lowering ECT Pulse Amplitude Increases Focality

Conventional Amplitude

\[ 0.8 - 0.9 \, \text{A} \]

Reduced Amplitude

\[ 0.1 - 0.4 \, \text{A} \]

Peterchev et al. JECT. 2010
Individualized Low Amplitude Seizure Therapy

- **Low amplitude** to spare nontarget brain regions contributing to cognitive side effects
- **Individualized** pulse amplitude to adjust for anatomical variation in induced E-field
- **Predict** dosage requirement
  - by motor threshold titration with TES for ECT, and with TMS for MST, or
  - by computational modeling of induced E-field
Low amplitude ECT – Proof of Concept

• Preclinical study
  – N=87 low current seizures in 4 NHPs
  – 4 different electrode placements
  – Current range 0.07-0.36 Amp

• Proof of concept open-label pilot
  – N=5 human pilot study
  – 0.5 Amp, RUL, 0.3 ms PW
  – Seizures induced in all patients
  – Demonstrated feasibility

Rosa et al. JECT. 2011
Amplitude Titration for Seizure Therapy

- Lowers brain volume exposed to suprathreshold fields
- Reduces inter-individual variability in dosage requirement

53-77%

19-33%

R01 MH091083; MPI: Lisanby / Peterchev
Amplitude Titration for Seizure Therapy

- Lowers brain volume exposed to suprathreshold fields
- Reduces inter-individual variability in dosage requirement
- Provides a novel means to predict individual dose requirement

Motor Threshold (mA)  Simulated E-field

\[ R^2 = 0.83 \]
\[ p = 0.0044 \]
• Zhi-de Deng – KL2 Awardee
• Project title “Individualized Optimal Targeting for Seizure Therapy”
• Mentors: Lisanby, McClintock
Working Model of ECT

Electric current applied through scalp electrodes to target brain areas associated with antidepressant action while minimizing stimulation of areas associated with side effects.

Applied current induces electric field in the brain.

Electric field induces a generalized, tonic-clonic seizure.

Seizure, in combination with tetanic electric stimulation, alter brain activity and connectivity, resulting in clinical & neurocognitive effects.
- Resting EEG connectivity maps (red - stronger; blue - weaker connectivity)
- Post-treatment changes in clustering coefficient and network density significantly higher in responders than nonresponders.

Aim 3. Assess the effects of focal and diffuse ECT on cortical excitability
• Conventional approach to dosing ECT in space should be re-thought.
• Reducing induced E-field with MST improves safety of seizure therapy without sacrificing efficacy
• ECT can approach focality of MST if low current amplitudes are used
• Anatomical variation can be compensated for by individualizing amplitude
• Motor threshold, or computational modeling of E-field, accurately predicts individual dosage requirements
The Persistence of Memory – Slavador Dali
Temporal Components of Dose

- Independent contributions of pulse and train parameters are obscured by summary metrics

Same Charge (mC)
Different Cognitive outcomes

Sackeim et al. 2008
Temporal Components of Dose

• Independent contributions of pulse and train parameters are obscured by summary metrics
• Calls for independent reporting of all pulse and train parameters to characterize dose
• Necessitates systematic testing of temporal parameters to optimize dosage
• Temporal Tuning
  – Pulse shaping
    • cTMS enables more efficient pulse configurations

[Diagrams and graphs showing pulse configurations and TMS systems]

Conventional TMS

- Controller
- Trigger
- Gate drive
- Amplitude
- Charger
- C
- D
- L

TMS pulse configurations:
- Pulse width control
- Directionality control

Normalized MEP size

Peterchev, Jalinos, & Lisanby 2008
• Temporal Tuning
  – Pulse shaping
  – Train optimization
    • Directionality
    • Frequency
      – Conventional dosage was inefficient
      – Points towards more efficient dosing strategies

Peterchev et al., In Preparation
• Conventional approach to dosing ECT in time should be re-thought.
• Re-shaping pulse improves potency of neuromodulation with subconvulsive rTMS
• Reducing train frequency increases efficiency of seizure induction with ECT and MST
Future challenges

- Understanding mechanisms of brain stimulation interaction with brain function across levels of analysis
  - Neuronal compartment
• How does TMS work at a neural level?
The Devil is in the Dosing
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Want to learn more?

- CME courses on TMS & ECT
  - Tara.Martin@duke.edu
- Electives
  - Clinical and research applications of brain stimulation

“Never, ever, think outside the box”