BRAIN Initiative
mapping brain activity at the speed of thought

http://braininitiative.nih.gov/
United States White House announced the “Next Great American Project”

“Giving scientists the tools they need to get a dynamic picture of the brain in action and better understand how we think and how we learn and how we remember. And that knowledge could be – will be – transformative.” — POTUS, April 2, 2013
New directions in science are launched by new tools more often than new concepts.

Concept-driven revolution explains old things in new ways.

Tool-driven revolution discovers new things that have to be explained.

Freeman Dyson

*Imagined Worlds, 1997*
• Large-scale *recording & modulation*  
  – at or near cellular resolution

**Modular nanophotonic probes for dense, large-scale neural recording with single-cell resolution**  
Roukes (PI, Caltech), Shepard, Siapas, Tolias
What’s the role of ECT in the BRAIN Initiative Era?
Electroconvulsive Therapy Circa 1938

- Dosing: One size fits all
- Used primarily for schizophrenia
- Limited knowledge of mechanism
- Excessive memory side effects
Electroconvulsive Therapy Circa 2018

- Dosing: Individualized
- Used primarily for depression
- Emerging knowledge of mechanism
- Reduced memory side effects
Evolution of ECT: 8 Decades of Progress
Evolution of ECT: 8 Decades of Progress?

Something, somewhere went terribly wrong.
ECT: Some Things **Don’t** Change
ECT: Some Things Don’t Change

- Highly Effective in
  - Reducing all cause mortality

Philibert 1995; O’Conner 2001; Kobeissi 2011
ECT: Some Things Don’t Change

- Highly Effective in
  - Reducing all cause mortality
  - Inducing remission from severe depression
- Prolonging Remission in Depressed Elders (PRIDE) NIMH sponsored study
  - N=222 depressed seniors
  - 83% remission rate among completers

U01 MH084241 [Kellner…Lisanby. Am J Psych 2016]
ECT: Some Things **Don’t Change**

- Highly Effective in
  - Reducing all cause mortality
  - Inducing remission from severe depression
  - Rapid onset of action

U01 MH084241 [Kellner...Lisanby. Am J Psych 2016]
ECT: Some Things Don’t Change

- Highly Effective in
  - Reducing all cause mortality
  - Inducing remission from severe depression
  - Rapid onset of action
  - Rapidly resolves suicidal ideation

0=A bsent
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

U01 MH084241 [Kellner...Lisanby. Am J Psych 2016]
ECT: Some Things Do Change

- Anesthesia
  - Protects body from motor convulsion and improves cardiovascular stability
ECT: Some Things Do Change

- Anesthesia
- Electrode Placements

Lisanby et al. Arch Gen Psych 2000
ECT: Some Things Do Change

- Anesthesia
- Electrode Placements

Lisanby et al. Arch Gen Psych 2000
Lee et al. Neuroimage 2012
ECT: Some Things Do Change

- Anesthesia
- Electrode Placements
- Pulse Shape

Sine Wave

Ultra-Brief Pulse

Brief Pulse

0.25-0.3 ms

1-2 ms

Amnesia Score (z)

RUL

BL

0.3 ms

0.3 ms

1.5 ms

1.5 ms

Ultra-Brief Pulse

Brief Pulse
ECT: Some Things Do Change

- Anesthesia
- Electrode Placements
- Pulse Shape

Ultra-Brief Pulse
0.25-0.3ms

Brief Pulse
1-2 ms

Current, I
Pulse Duration

Ultra-Brief Pulse

Brief Pulse

Agnew & McCreery, 1990
ECT: Some Things Do Change

- Anesthesia
- Electrode Placements
- Pulse Shape
- Individualizing dosage
  - From “one size fits all”, to
  - Age-based dosing, to
  - Seizure threshold titration

Sackeim et al., 2000
Lessons Learned: Dosage Matters

- For efficacy
- For safety

Sackeim et al. Arch Gen Psych 2000
McCall et al. Arch Gen Psych 2000
Lessons Learned: Dosage Matters

- For efficacy
- For safety

Dissociable
Lessons Learned: **Dosage Matters**

- For efficacy
- For safety

Sackeim et al., 2000; Nobler et al. 1994; Luber et al. 2000
Lessons Learned: **Dosage is Complicated**

- Electrode Placement
  - Spatial distribution

Lee et al., EMBC14
Lessons Learned: **Dosage is Complicated**

- **Electrode Placement**
  - Spatial distribution
  - Novel electrode placements

Lee et al., ISEN 2012; Rosa et al JECT 2011
• ECT E-field exceeds neural activation threshold by >2 times and stimulates > 94% of brain volume, much higher than necessary for seizure induction

• FEAST and FM more focal and closer to threshold stimulation

• MST induces weakest, most superficial E-field, stimulating only 4% of brain volume

Lee et al., EMBC14
Lessons Learned: **Dosage is Complicated**

- **Electrode Placement**
  - Spatial distribution
  - Novel electrode placements possible
  - Multi-electrode arrays for E-field shaping

![Conventional vs High Def RUL](image.png)
Lessons Learned: **Dosage is Complicated**

- **Electrode Placement**
- **Pulse Shape**
  - Pulse Width

- **Ultra-Brief Pulse**: 0.25-0.3ms
- **Brief Pulse**: 1-2 ms
Lessons Learned: **Dosage is Complicated**

- Electrode Placement
- Pulse Shape
  - Pulse Width

**Interaction**

Shortening the pulse width undoes the efficacy of bilateral electrode placement

Brain Stimulation (2008) 1, 71–83
Lessons Learned: **Dosage is Complicated**

- Electrode Placement
- Pulse Shape
  - Pulse Width
  - Waveform

**Conventional**

**Biphasic**
- Charge balanced

**Pre-polarization**

**Multiphasic**
- Charge balanced, but predominantly monophasic

Lessons Learned: **Dosage is Complicated**
Lessons Learned: **Dosage is Complicated**

- Electrode Placement
- Pulse Shape
  - Pulse Width
  - Waveform
  - Amplitude

Conventional Amplitude

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

Reduced Amplitude

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

Peterchev et al. JECT. 2010
Lessons Learned: **Dosage is Complicated**

- **Electrode Placement**
- **Pulse Shape**
  - Pulse Width
  - Waveform
  - Amplitude

**Interaction**

Lowering amplitude improves focality

Opportunity to dissociate efficacy from side effects

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R01 MH091083; MPI: Lisanby / Peterchev
Peterchev et al. Neuropsychopharmacology 2015
Lessons Learned: **Dosage is Complicated**

- Electrode Placement
- Pulse Shape
- Total Delivered Charge
  - milliCoulombs (mC)
Lessons Learned: **Dosage is Complicated**

- Electrode Placement
- Pulse Shape
- Total Delivered Charge
  - milliCoulombs (mC)

Sackeim et al. 2008

Same Charge (mC)  
Different Cognitive outcomes
Lessons Learned: **Dosage is Complicated**

- Electrode Placement
- Pulse Shape
- Total Delivered Charge
  - milliCoulombs (mC)

Same Charge (mC)  
Different Cognitive outcomes

*Sackeim et al. 2008*
Lessons Learned: **Dosage is Complicated**

- Electrode Placement
- Pulse Shape
- Total Delivered Charge
  – milliCoulombs (mC)

**Interaction**

- RUL less effective than BL when given at low dose
- 6x threshold RUL as effective as BL
Lessons Learned: **Dosage is Complicated**

- Electrode Placement
- Pulse Shape
- Total Delivered Charge
- Individual Parameters
  - Matter

![Diagram showing pulse parameters](image)
Lessons Learned: **Dosage is Complicated**

- Electrode Placement
- Pulse Shape
- Total Delivered Charge
- Individual Parameters
  - Matter
  - Should be individually optimized
Lessons Learned: **Dosage is Complicated**

- Electrode Placement
- Pulse Shape
- Total Delivered Charge
- Individual Parameters
  - Matter
  - Should be individually optimized, eg.
    - Frequency

R01 MH091083; MPI: Lisanby / Peterchev
Lessons Learned: **Dosage is Complicated**

- Electrode Placement
- Pulse Shape
- Total Delivered Charge
- Individual Parameters
  - Matter
  - Should be individually optimized, eg.
    - Frequency
    - Directionality

Lessons Learned: Dosage is Complicated

Spellman, Peterchev, Lisanby 2009
Lessons Learned: **Dosage is Complicated**

- Electrode Placement
- Pulse Shape
- Total Delivered Charge
- Individual Parameters
  - Matter
  - Should be individually optimized
  - Interactions among parameters should be examined

**Electroconvulsive Therapy Stimulus Parameters**

*Rethinking Dosage*

Angel V. Peterchev, PhD,*† Moacyr A. Rosa, MD, PhD,* Zhi-De Deng, MEng,*† Joan Prudic, MD,* and Sarah H. Lisanby, MD*  

J ECT 2010
Device Design

Conventional Approach

- Computational Models
- Stimulation
- Device
- Parameters

Rational Approach

- Clinical Trials
  - Revise stimulation paradigm
  - Open Label Randomized Trials
  - Clinically test each stimulation paradigm

Animal & Healthy Human Studies
Lessons Learned: **Relapse Prevention**

- **Prolonging Remission in Depressed Elders (PRIDE)**
  - NIMH-funded U01 (PIs: Lisanby and Kellner)
  - 8 centers across the United States
  - 1,326 patients screened, 240 enrolled
  - Mean age $70 \pm 8$ yrs, 58% female

_Kellner .... Lisanby. Am J Psych 2016a,b_
Lessons Learned: **Relapse Prevention**
Lessons Learned: **Relapse Prevention**

- **Prolonging Remission in Depressed Elders (PRIDE)**
- **Aims:** To compare efficacy and tolerability of 2 post-ECT continuation treatment strategies:
  - PHARM - venlafaxine (VLF) + Li
  - STABLE - Symptom titrated algorithm based longitudinal ECT

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**Phase 1**

- ECT+VLF
- Remitters
- Nonremitters

**Phase 2** (6 mo)

- C-ECT (STABLE)+VLF+Li
- VLF+Li
- CR, F/T (Bsl Ph 2)
- CR, F/T at specified time points (see Table 3)

**Fig 5. PRIDE Trial Design**

F/T = functional and tolerability ratings
Prolonging Remission post ECT

Kellner …. Lisanby. Am J Psych 2016a,b

- Probability of Maintaining Remission
- 20.3% relapsed
- Odds of relapse 1.7x higher than STABLE
- 13.1% relapsed
- STABLE
Lessons Learned: Emerging Evidence of Mechanism

- Emerging biomarkers of response show regional specificity

Abbott et al. 2014
Lessons Learned: Emerging Evidence of Mechanism

- Emerging biomarkers of response show regional specificity
- ECT modalities differ in their regional effects
Lessons Learned: Emerging Evidence of Mechanism

- Unknown if hippocampal stimulation may also contribute to side effects, or efficacy, or both
- ECT Induces and saturates LTP
- Hypothesized role in ECT-induced amnesia

Stewart & Reid 1993; SteCasarotto et al 2013
ECT: Some Things Still Need To Change

• Stigma
What will the future of ECT look like?

• Safer
• Faster
• Longer-lasting
• Less need for anesthesia?
  – Weaker or no motor convulsion

Old Dog – New Trick
Roadmap for Getting There

• Target Discovery
  – Understanding mechanisms of therapeutic action and adverse cognitive side effects

• Advanced Tools
  – Advances in seizure induction technique to optimize spatial and temporal resolution

• Experimental Trials
  – Testing that reaching and engaging specific targets will result in improved clinical outcomes for depression
NIMH Noninvasive Neuromodulation Unit

Special Thanks to ETPB Medical and Nursing staff, George Dold, Bruce Pritchard, and the Section on Instrumentation

ETPB Shared Staff: Shora, Yu
NIAAA Collaborator: Ted George
Summer Student: Michael Dib
Coming Sept 2018: Michele Noh (Deng NARSAD YIA)
Rationale for UltraBrief Pulse

- Closer to chronaxie
- More efficient stimulus means seizure induced with lower total E-field exposure
- Different time constants between soma and axon
- Briefer pulse widths less stimulation of cell bodies

Peterchev & Lisanby, unpublished