Deep Brain Stimulation for Mood and Anxiety Disorders
Progress, Challenges, Future Directions

Alik Widge, MD, PhD
Translational NeuroEngineering Laboratory
University of Minnesota

awidge@umn.edu
http://www.tnelab.org

@AlikWidge
Disclosures

• Financial Conflicts:
  – Device donations & minor consulting, Medtronic
  – Consulting, Livanova & Circuit Therapeutics

• Off-Label/Investigational Device Use:
  – Deep brain stimulation for depression

• Support for work discussed today:
  – Picower Foundation
  – DARPA BTO/SUBNETS
  – NIMH, NINDS
  – Brain & Behavior Research Foundation
  – OneMind Institute
  – MnDRIVE/Medical Discovery Team - Addictions

The views throughout this talk are my own, not those of the sponsors/manufacturers.
Take-Home Points

• DBS has promising early evidence and mixed RCT results, still investigational except for OCD
  — Genuine evidence of biological signal
  — Side effects, stochastic efficacy remain problems

• Mechanistic understanding needed, some evidence for improved executive function

• Technology rapidly advancing, “closed loop” methods now in early trials
Overview / Roadmap

- Technology, Targets, and Populations
- Clinical Trial Outcomes
- Progress Towards Improvement
  - Mechanistic Understanding
  - Advanced Stimulation Strategies
- Discussion
Deep Brain Stimulation

- Large wire surgically implanted in brain
- Pulse generator and battery in chest
- Clinician adjusts by RF communication with the IPG
- “Brain pacemaker”
Disorders Tested to Date

• Focus on major depressive disorder (MDD) and obsessive-compulsive disorder (OCD)
• MDD=most common disorder with wide economic impact
• OCD=one of the rare disorders where dx is clear-cut and relatively homogeneous
Psych DBS In 2019: Three Targets*

Ventral Capsule/
Ventral Striatum
Malone et al. 2009

Depression and OCD

Brodmann Area 25 (Cg25)
Holtzheimer et al. 2012

Depression, including
Bipolar

Medial Forebrain Bundle
Schlaepfer et al. 2013

Depression
It’s Not Brain Surgery

- Severely ill: YBOCS > 30/40, MADRS > 28/60, HAMD-17 > 20/50
- Failed multiple treatments: meds (multiple classes), CBT, ECT
  - Provably adequate dose/duration trials
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Framework: Hype Cycle

Widge et al., *Frontiers* 2018
Open Label: Depression (VC/VS)

Malone et al. 2009
Open Label: OCD (VC/VS)

Greenberg et al. 2010
Framework: Hype Cycle

Peek of Inflated Expectations

Start

Visibility

Technology Maturity

Widge et al., Frontiers 2018
RCT: Depression (VC/VS, RECLAIM)

Dougherty et al. 2015
RCT: Depression (Cg25, BROADEN)

Mean MADRS score by study visit

All participants receiving active treatment

Holtzheimer et al. 2017
Framework: Hype Cycle

Start

Peak

Valley of Despair

Visibility

Technology Maturity

Widge et al., *Frontiers* 2018
Hope: Study Design Innovation

- VC/VS success in MDD: 52-week open-label \textit{then} sham crossover

Bergfeld et al. 2016
Hope: Study Design Innovation

• VC/VS success in OCD: optimize, then blinded cross-over

Luyten et al. 2016
## Summary: 2019 State of Evidence

<table>
<thead>
<tr>
<th>Site</th>
<th>VC/VS</th>
<th>Cg25</th>
<th>MFB</th>
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<tr>
<td>Open-Label</td>
<td>MDD, OCD</td>
<td>MDD</td>
<td>MDD</td>
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<td>RCT Evidence</td>
<td>1/2 MDD, 1/2+ OCD</td>
<td>0/1 MDD</td>
<td>Ongoing</td>
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<tr>
<td>Legal Status</td>
<td>HDE for OCD only</td>
<td>Investigational</td>
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Challenges: Heterogeneity, Hypomania

- Psychological complications in ~50% across targets
- High response variability
- Effective "dose" quite unclear
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  - **Progress Towards Improvement**
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Framework: Hype Cycle

Visibility

Technology Maturity

Start

Peak

Valley

Slope of Enlightenment

Widge et al., *Frontiers* 2018
Overview / Roadmap

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• Clinical Trial Outcomes
• Progress Towards Improvement
  • Mechanistic Understanding
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Sam Zorowitz
Now PhD student, Princeton Neuroscience Institute
Nosology Probably Not Helping

DA Regier et al 2013
DSM-5 Field Trials

Widge et al.,
Experimental Neurology 2017
Common Domains Across Syndromes

- VC/VS target used for depression and OCD
- Lesions in related structures work too
- Shared dysfunctions?
  - Rigid, inflexible thinking
  - Strong, overwhelming emotions
  - Risk-driven decision-making
Common Domains, Common Circuits

Haber & Heilbrunner 2013
Cg25 Hits Similar Network

Riva-Posse et al. 2014
“Stress Testing” Flexibility Circuits

- Multiple Source Interference Test
- “Press the number that is different”
Experiment Design (EMOTE-DBS)

N=14 for behavior, N=8 usable EEG
12 MDD and 2 OCD

Widge, Zorowitz, et al., *Nature Communications*, forthcoming
VC/VS DBS Improves Flexibility

Not just a motor effect!

40.12 ms, 
t=-2.136, p=0.033

0.03 Hz, 
t=0.857, p=0.391
Theta (5-8 Hz) Changes in PFC
Broad Fronto-Cingulate Network
What Does This Mean?

• DBS (esp VC/VS) might improve processing of complex/conflicting information
• “Grease the wheels”, pt more mentally flexible, able to learn new skills/thoughts
Continuum vs. Separable Axes

Model A, “Continuum”

Model B, “Dimensional”

Flexibility

Stuck Thinking
Wellness
Hypomania

Impulsivity

Perseveration
Hypomania

Stuck Thinking
Wellness

“Good” DBS
“Bad” DBS
“Good” DBS
“Bad” DBS
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M. Taha Bilge
Alex Rockhill
Anish Kanabar
Multi-Point, Circuit Stimulation

Hyperactive CSTC loop circuitry and neurosurgical interruption

Coherent oscillations for (hyper)communication

Dougherty et al., *JAMA Psychiatry* 2018

Fries 2005 & Fries 2015
Chronic Coherence x Stim In Human
Subjective Response to Disruption

• Subject PCS01
• Prior DBS for OCD, partial responder
  – Extensive prior experience with stim
• Converted to dual-site implant
• 3 months open label lead-in, then blinded-onset initiation
Subjective Response to Disruption

Combined Cortical–Subcortical Stimulation in OCD
Patient PCS01
Subjective Improvement During Cortical Mapping

Alik Widge, MD PhD / Darin Dougherty, MD / M. Taha Bilge, PhD

MGH 1811
TNE LAB
University of Minnesota
Driven to Discover®
Large, Long-Lived Eruption
Overview / Roadmap

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Take-Home Points

• Investigational, but evidence building
  – “Back end” trial designs revealing signal
  – Response rate still low for a surgical therapy
• Cross-diagnostic/RDoC approach may be fruitful for understanding mechanisms
• New technologies offer potentially greater efficacy, circuit/physiology directed
## Acknowledgements

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<th>MGH/MIT</th>
<th>- Ishita Basu</th>
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<td>- Sydney Cash</td>
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\[ X(t) = X(t - 1) + B(u(t)) \]

\[ B(s) = \frac{sX(s)}{u(s)} \]