NEURONETICS

Non-Invasive Neuromodulation of the Central Nervous System

Part Two: Developing Non-Invasive Neuromodulation Devices for Therapeutic Uses

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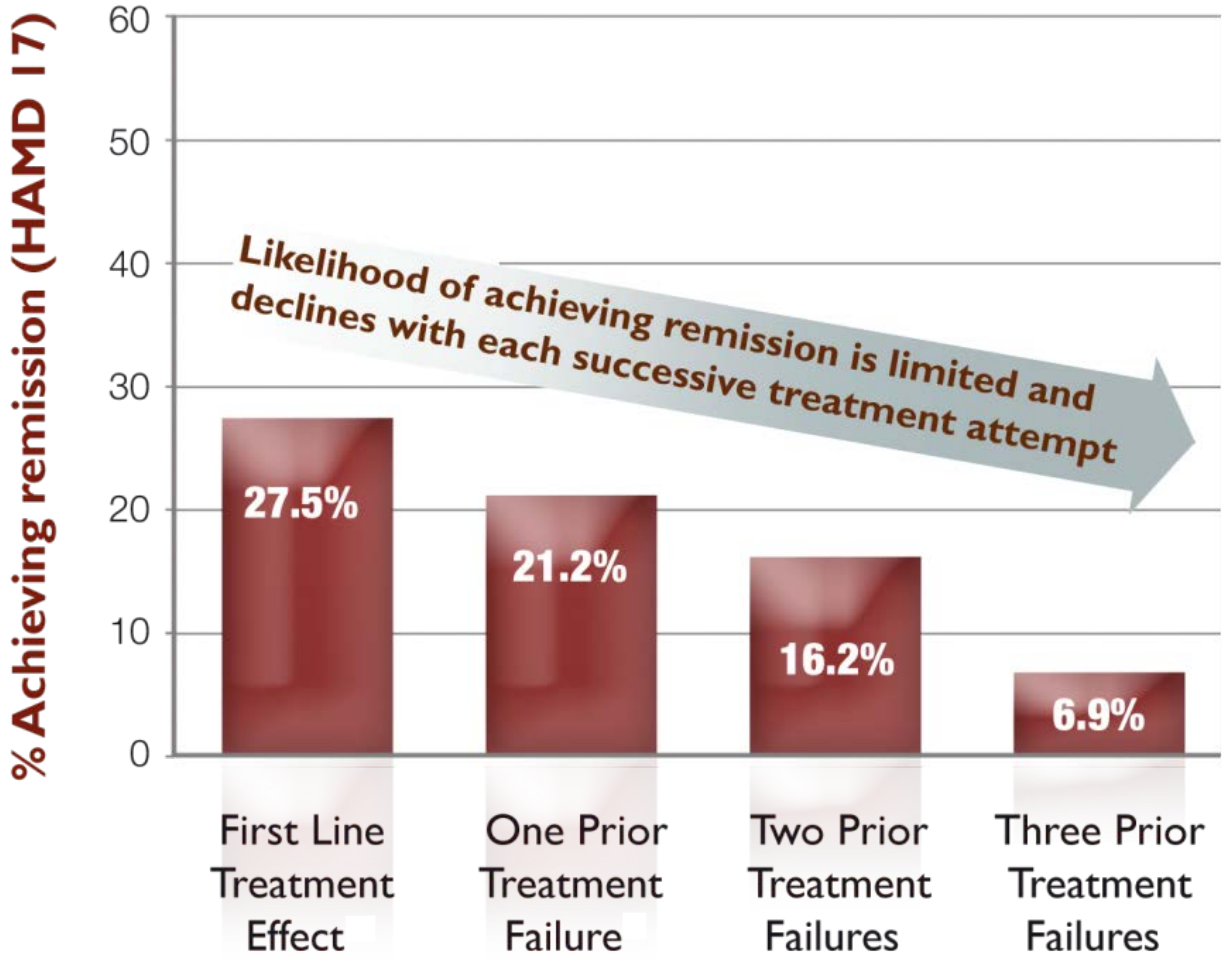
Questions

- *What is the level of interest in development of these devices?*
- *What are the opportunities and barriers to development?*

Opportunities

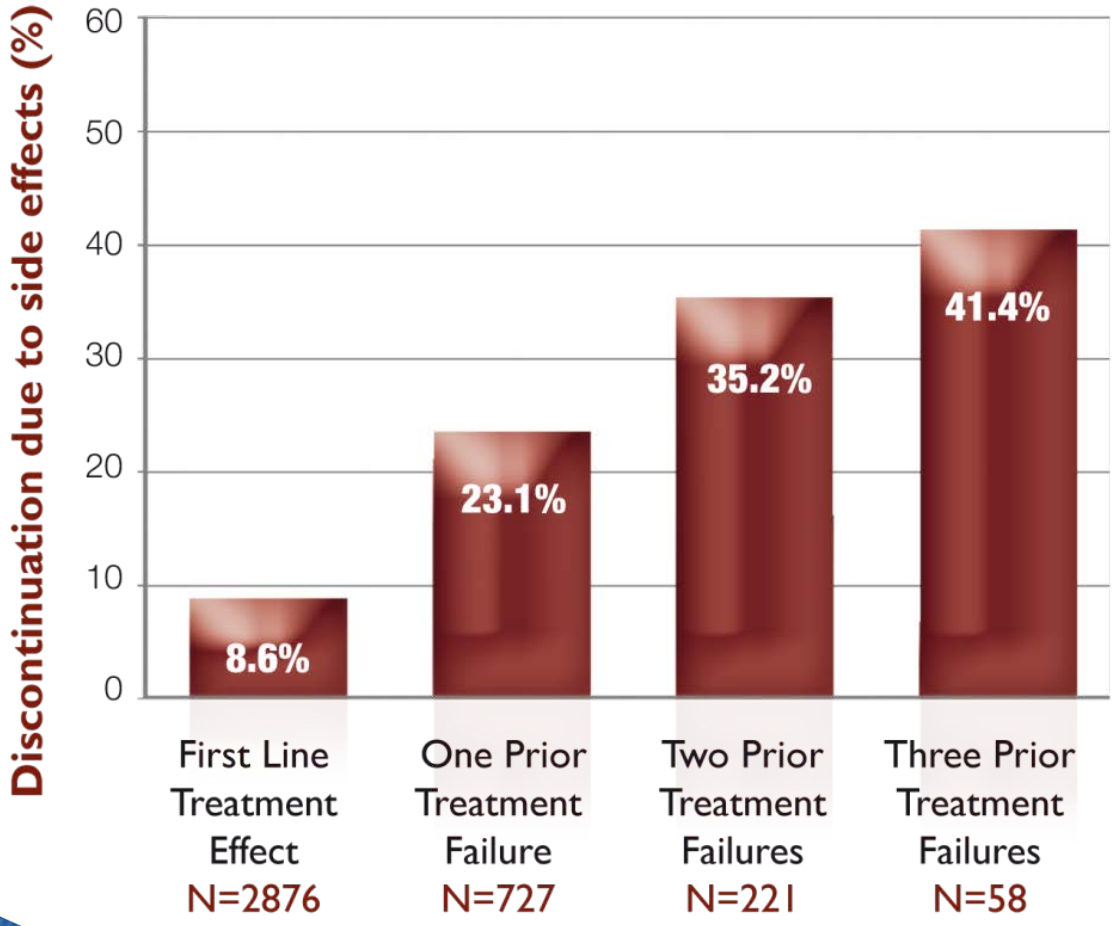
- Current treatment options are insufficient
- Emerging models of psychiatric disease as network-based pathology
- The brain is responsive to electrical and chemical modification
- The evidence base for effective treatment is substantial (e.g., TMS Therapy)
- The reimbursement landscape is changing rapidly
  - Over 200 million covered lives for TMS in the US

STAR*D Study demonstrates that current treatments have limited effectiveness



Trivedi (2006) *Am J Psychiatry*; Rush (2006) *Am J Psychiatry*; Fava (2006) *Am J Psychiatry*; McGrath (2006) *Am J Psychiatry*

Likelihood of discontinuing treatment increases with each new medication attempt



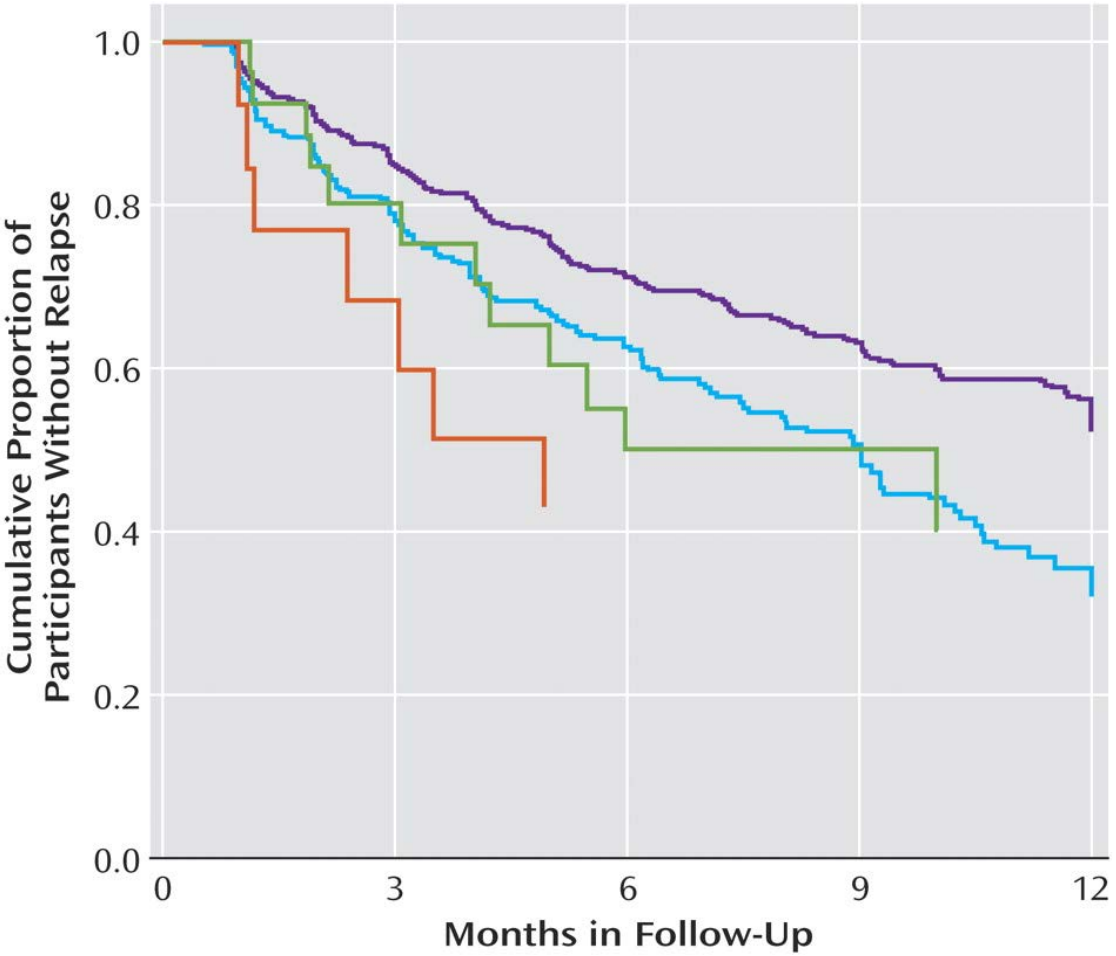
Systemic Drug Side Effects

- Weight Gain
- Constipation
- Diarrhea
- Nausea
- Drowsiness
- Insomnia
- Decreased Libido
- Nervous Anxiety
- Increased Appetite
- Decreased Appetite
- Fatigue
- Headache/ Migraine
- Abnormal Ejaculation
- Impotence
- Sweating
- Tremor
- Treatment Discontinuation Side Effects
- Weakness
- Dry Mouth
- Dizziness

Trivedi (2006) *Am J Psychiatry*; Rush (2006) *Am J Psychiatry*; Fava (2006) *Am J Psychiatry*; McGrath (2006) *Am J Psychiatry*; Neuronetics, Inc. (data on file)

Relapse During Long-Term Follow-Up

*STAR*D Study Results*



The higher the level of treatment resistance prior to remission, the faster the relapse in long term follow up

- **Level 1 (non-resistant)**
- **Level 2 (1 prior Tx failure)**
- **Level 3 (2 prior Tx failures)**
- **Level 4 (3 prior Tx failures)**

Rush, (2006)

NeuroStar TMS Therapy Modulates Discrete Deep Brain Regions

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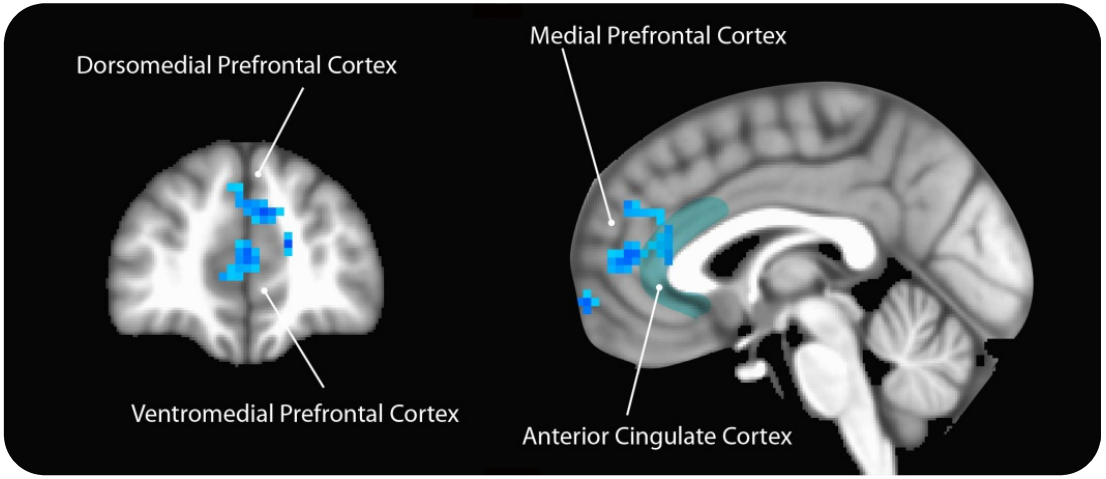
PRIORITY COMMUNICATION

Default Mode Network Mechanisms of Transcranial Magnetic Stimulation in Depression

Conor Liston, Ashley C. Chen, Benjamin D. Zebley, Andrew T. Drysdale, Rebecca Gordon, Bruce Leuchter, Henning U. Voss, B.J. Casey, Amit Etkin, and Marc J. Dubin

- Treatment reduces hyperconnectivity within the default mode network (VMPFC, Ant Cingulate)



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NeuroStar TMS Practice Locations

Over 630 Systems Installed

CPT Category I Codes for TMS
Effective since January 1, 2012

90867	• Therapeutic repetitive transcranial magnetic stimulation treatment; initial, including cortical mapping, motor threshold determination, delivery and management
90868	• Subsequent delivery and management, per session
90869	• Subsequent MT re-determination with delivery and management

Source: Current Procedural Terminology 2012, American Medical Association CPT is a Registered Trademark of the American Medical Association

Evidence Base for Efficacy of TMS is Acknowledged in AHRQ Final Report

- Independent, Peer-reviewed
- Tier 1 studies of TMS: 15 clinical trials involving nearly five hundred patients
  - Average HAMD decrease in depressive symptoms > 5 points vs. sham control
    - » Meets minimum clinical significance threshold of 3 points on the HAMD scale
  - Response rates >3x as likely than sham control
  - Remission rate >6x as likely than sham control
- ***"High strength of evidence" for efficacy from well-controlled RCTs***

Agency for Healthcare Research and Quality: Comparative Effectiveness Report on Non-Pharmacologic Treatments for Depression , October 2011

TMS is Included in Practice Guidelines
Following Failure of Initial Treatment

Guideline Sources

American Psychiatric Association (2010)

"…Acute phase treatment may include pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or light therapy…"

World Federation of Societies for Biological Psychiatry (2009)

Canadian Network for Mood and Anxiety Treatments (2009)

Royal Australia and New Zealand College of Psychiatrists (2013)

Schlaepfer, et al. *World J Biol Psychiatry* (2009); Kennedy, et al *J Aff Disorders* (2009); American Psychiatric Association (2010)

Barriers

- **A consensus taxonomy of neuromodulation is needed**
- The paradigm is new; Awareness/understanding is very low
- Technical understanding of mechanisms of effect is lacking
- Practitioners tend to resist change in practice methods (“Clinician Inertia”)
- There are few professional organizations dedicated to addressing the needs of the emerging clinical science
- Interests of researchers and clinical practitioners are not aligned
- Funding sources for innovative research are limited
- Establishing evidence-based practice is challenging in a “DIY” environment
- Clinical trial methods for device-based treatments are lacking
- What is the business model?