

Stimulation and Surgical Approaches to Psychiatric Illness

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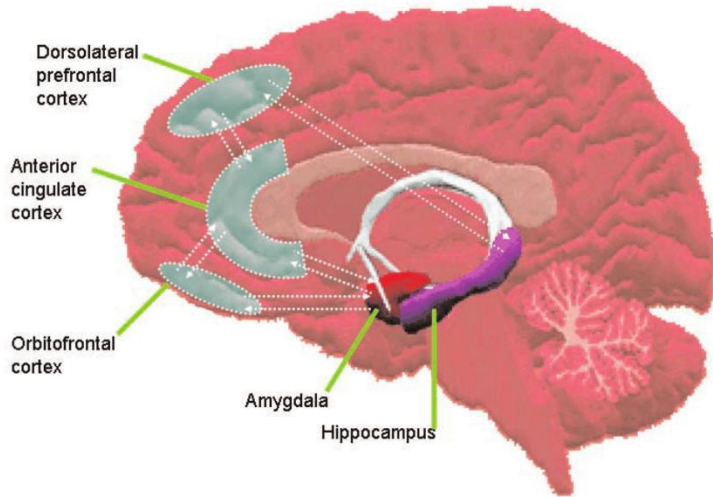
Associate Professor of Psychiatry
Harvard Medical School

Disclosures

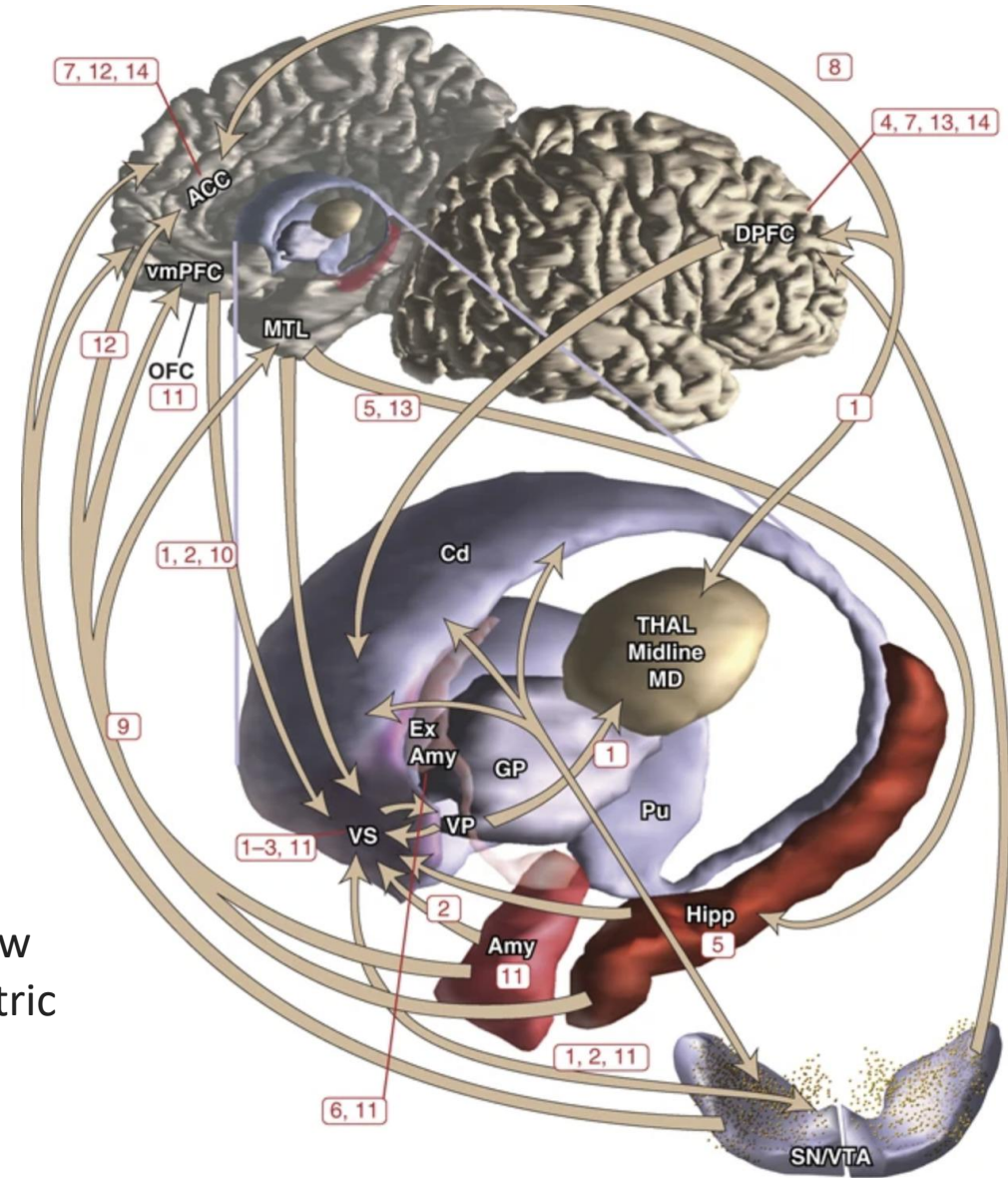
Cristina Cusin 2022-2026:

- **Speaking/CME/Consulting:** Perception, Compass, Clexio, Boehringer
- **Research Grants:** Livanova, ATAI, Abbott
- **Equity:** None
- **Royalty/patent:** PCT/US15/56192; 070919.00032 Acylcucurbit[N]uril type molecular containers to treat intoxication and substance abuse
 - Springer (book on TRD)

Depression Model



Haber, S., Rauch, S. Neurocircuitry: A Window into the Networks Underlying Neuropsychiatric Disease. *Neuropsychopharmacol* **35**, 1–3 (2010).



Psychiatric Neurotherapeutics

Definition = surgical & device-based treatments

- Electroconvulsive therapy (ECT) –circa 1920
- Vagus Nerve Stimulation (VNS) – circa 1990S
- Transcranial Magnetic Stimulation (TMS)
- Psychiatric Neurosurgery
 - Lesion (ablative) procedures – circa 1900s
 - Deep Brain Stimulation (DBS)

ECT - Just a bit of History

- 1930s Lazlo Meduna observed temporary remission of 'schizophrenic'* symptoms after epileptic seizure
- inducing convulsions with injectables in psychiatric patients (camphor, pentylenetetrazol, insulin)
- 1938 Cerletti and Bini developed a device to induce seizure via electricity
- Successful application in catatonia (luck, mostly Bp patients)
- 1950's- ether and curare extract developed ('modified ECT')

ECT Indications

Severe MDD/ BP Depression/ BP Mania

Acute SI /refusal of food/ rapidly deteriorating

Psychosis

Catatonia, Neuroleptic Malignant Syndrome

Depression/ Psychosis during **pregnancy**

Treatment Resistant Schizophrenia

Efficacy as Antidepressant

- 2003 – UK ECT Review Group
- **Real vs Sham ECT on Depression:**
 - 6 trials, 256 patients, 2 sine wave
 - Mean difference HDRS 9.7 (95% CI 5.7-13.5)
- **Bilateral vs Unilateral ECT:**
 - 22 trials, 1408 patients, Duration, Placement, Number varied
 - Mean difference HDRS 3.6 (95% CI 2.2- 5.2) - Bilateral
- **ECT vs Pharmacotherapy:**
 - 18 trials, 1144 patients, Duration, Placement, Number varied
 - Mean difference HDRS 5.2 (95% CI 1.4 – 8.9)
 - TCA's, MAOI's, Tryptophan, SSRI's, Li
 - Variable definitions of treatment refractoriness (4 trials).

*e.g., UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: A systematic review and meta-analysis. *Lancet* 2003;361:799-808.

ECT PROS

- ‘Gold standard’ for TRD, response 50-75%.
- Efficacy and tolerability vary according to impulse parameters, electrode placement, stimulus intensity and number and frequency of treatments
- Efficacy vary based on stimulus intensity/seizure threshold of individual patient at that time (extreme intra-subject variability x20)

UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: A systematic review and meta-analysis. Lancet 2003;361:799-808

ECT CONS

- High risk of relapse (60 % at 6 months, 85% in absence of pharmacotherapy) -> may need maintenance ECT for a while
- Significant burden, time (8-12 treatments, x2-3 per week, then lower frequency)
- Hospital setting, costs, exposure to anesthesia, and risk of side effects, esp. amnesia
- Extent and duration of longer-term cognitive side effects highly variable

Cognitive Side effects of ECT

- Neurocognitive pattern of ECT-related **memory** impairments consistent with memory loss associated with temporal lobe epilepsy (TLE), with possible disruption of **storage and/or retrieval processes** dependent on the hippocampus, parahippocampal gyrus, and related diencephalic structures.
- Preserved priming, skill acquisition, and other procedural memory abilities.
- strong evidence that **retrograde amnestic** effects of ECT may have frontal lobe involvement

Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. Sackeim et al. N Engl J Med. 1993

Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. Semkovska M and McLoughlin DM Biol Psychiatry. 2010 Sep 15; 68(6):568-77.

Vagal Nerve Stimulation (VNS)

- An electrode attached to the nerve in the neck, coupled to a pulse generator implanted in the chest wall.
- Vagus Sensory Afferents Go to Midbrain, Limbic, and Prefrontal Structures
- Serendipitous discovery of effect on mood in patients with epilepsy
- FDA- approved for treatment-refractory epilepsy and TRD
- (About 130 K for surgery and device)

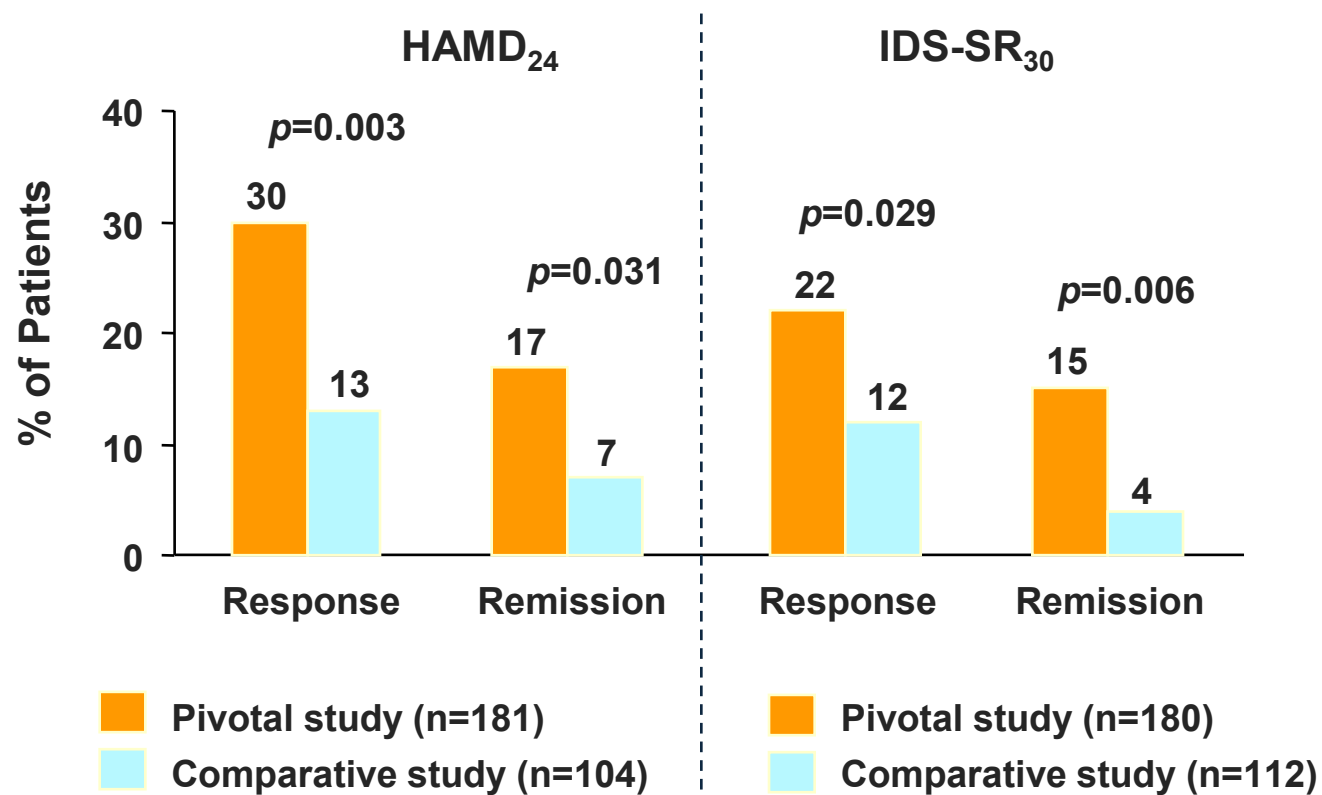
- increase serotonergic and noradrenergic transmission in the brain, ?
improve limbic system blood flow
- Adverse effects in the post-operative period include pain, cough, vocal cord paralysis, hoarseness, and nausea

VNS for TRD

- Approved by FDA for TRD in 2005 despite primary outcome measure (active versus sham) difference at 8 weeks being $p=0.06$. Ultimately approved based on secondary outcome measures (next slide)
- Insurers have used this to classify VNS for TRD as investigational despite FDA approval and reimbursement success is currently 35-40% with private insurers after 6-9 months of appeals

Pivotal Study Versus Comparative Study: Secondary Analysis

HAMD₂₄ and IDS-SR₃₀ Categorical Outcomes at 12 Months (Observed Cases)



VNS outcomes at 5 years

A 5-Year Observational Study of Patients With Treatment-Resistant Depression Treated With Vagus Nerve Stimulation or Treatment as Usual: Comparison of Response, Remission, and Suicidality

Scott T. Aaronson, M.D., Peter Sears, C.C.R.P., Francis Ruvuna, Ph.D., Mark Bunker, Pharm.D., Charles R. Conway, M.D., Darin D. Dougherty, M.D., Frederick W. Reimherr, M.D., Thomas L. Schwartz, M.D., John M. Zajecka, M.D.

Objective: The Treatment-Resistant Depression Registry investigated whether adjunctive vagus nerve stimulation (VNS) with treatment as usual in depression has superior long-term outcomes compared with treatment as usual only.

Method: This 5-year, prospective, open-label, nonrandomized, observational registry study was conducted at 61 U.S. sites and included 795 patients who were experiencing a major depressive episode (unipolar or bipolar depression) of at least 2 years' duration or had three or more depressive episodes (including the current episode), and who had failed four or more depression treatments (including ECT). Patients with a history of psychosis or rapid-cycling bipolar disorder were excluded. The primary efficacy measure was response rate, defined as a decrease of $\geq 50\%$ in baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score at any post-baseline visit during the 5-year study. Secondary efficacy measures included remission.

Results: Patients had chronic moderate to severe depression at baseline (the mean MADRS score was 29.3 [SD=6.9] for the

treatment-as-usual group and 33.1 [SD=7.0] for the adjunctive VNS group). The registry results indicate that the adjunctive VNS group had better clinical outcomes than the treatment-as-usual group, including a significantly higher 5-year cumulative response rate (67.6% compared with 40.9%) and a significantly higher remission rate (cumulative first-time remitters, 43.3% compared with 25.7%). A subanalysis demonstrated that among patients with a history of response to ECT, those in the adjunctive VNS group had a significantly higher 5-year cumulative response rate than those in the treatment-as-usual group (71.3% compared with 56.9%). A similar significant response differential was observed among ECT nonresponders (59.6% compared with 34.1%).

Conclusions: This registry represents the longest and largest naturalistic study of efficacy outcomes in treatment-resistant depression, and it provides additional evidence that adjunctive VNS has enhanced antidepressant effects compared with treatment as usual in this severely ill patient population.

Am J Psychiatry 2017; 174:640–648; doi:10.1176/appi.ajp.2017.16010034

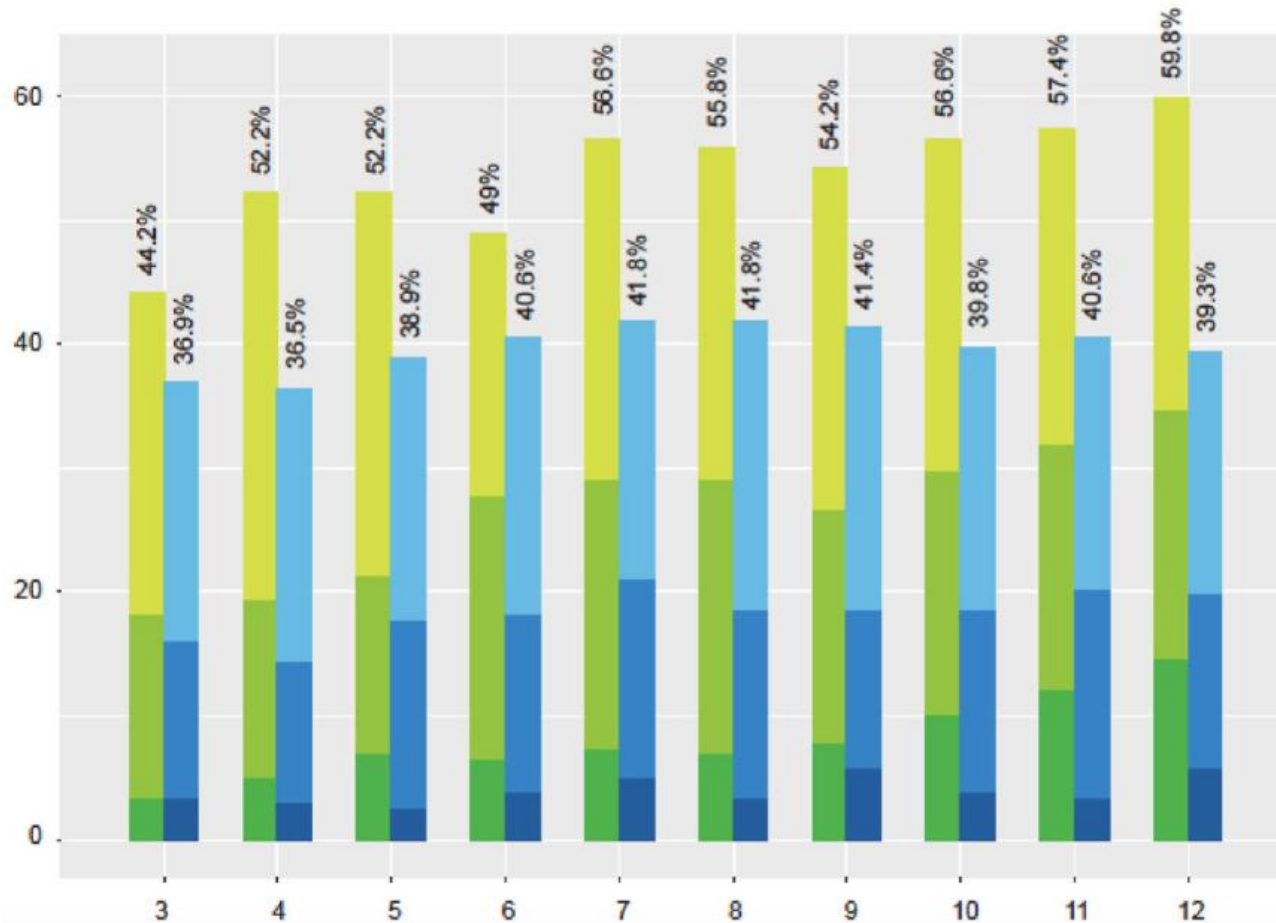
Prospective serial depression treatment trials demonstrate that more than 60% of patients with major depressive disorder fail to remit with an initial pharmacotherapy trial, and

resulting in a large population of symptomatically and functionally impaired individuals (1, 5).

Vagus nerve stimulation (VNS) has been shown to be

VNS most recent data

PR w/o Resp Off PR w/o Rems Off Rems Off
PR w/o Resp On PR w/o Rems On Rems On



500 participants at 84 sites
12 months, double blind, sham controlled
On average failed 13 treatments

Charles R. Conway et al, Vagus Nerve Stimulation in Treatment-Resistant Depression: A One-Year, Randomized, Sham-Controlled Trial, *Brain Stimulation* (2024)

VNS access

- Most insurers refuse to cover VNS, limited success with commercial payers
- Patients have failed 4+(8-10) ADs, 50% has failed ECT
- RCT sponsored by Livanova and Medicare available for patients with Medicare (RECOVER, 5 years, 1 yr of double blind, 400 MDD + 400 BPdep)
- VNS seems Increasingly effective over time
- Battery lasts 10 ys
- Most patients continue to take their meds
- Can replace maintenance ECT

General Principles of TMS

- magnetic field applied to scalp surface to generate electrical stimulation of focal areas of brain cortex
- Unlike ECT, does not involve general anesthesia or seizures, No restrictions on activity especially driving
- Approved by US FDA for use in treatment of depression and OCD
- Initial treatment course: **five daily treatment per week (M-F) for 4-6 weeks.** Daily treatment duration: 3 - 30 minutes
- Taper period: 1-3 treatments per week
- Usually long gap before insurance authorizes it again - relapse

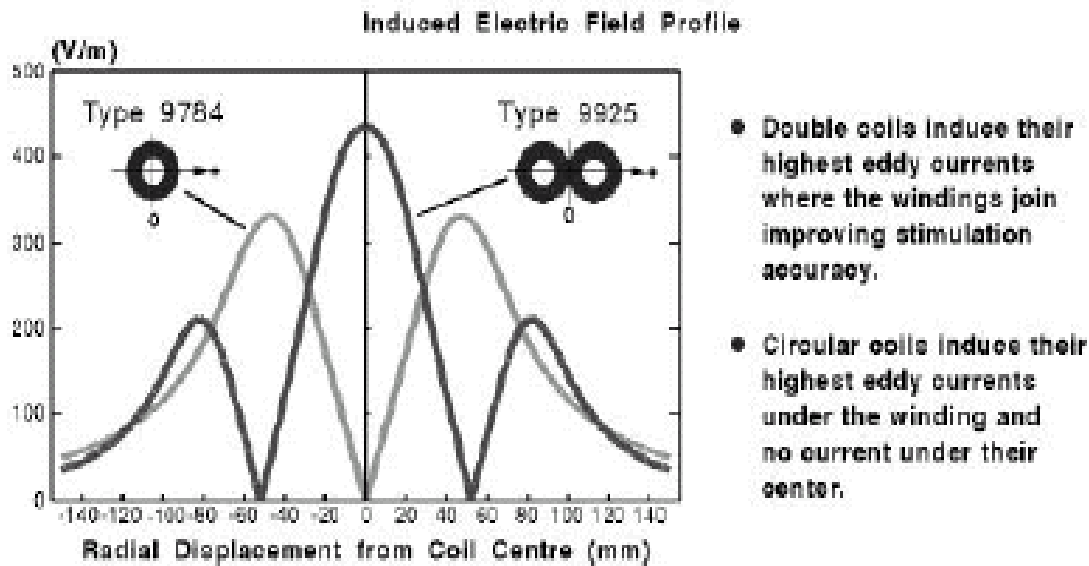
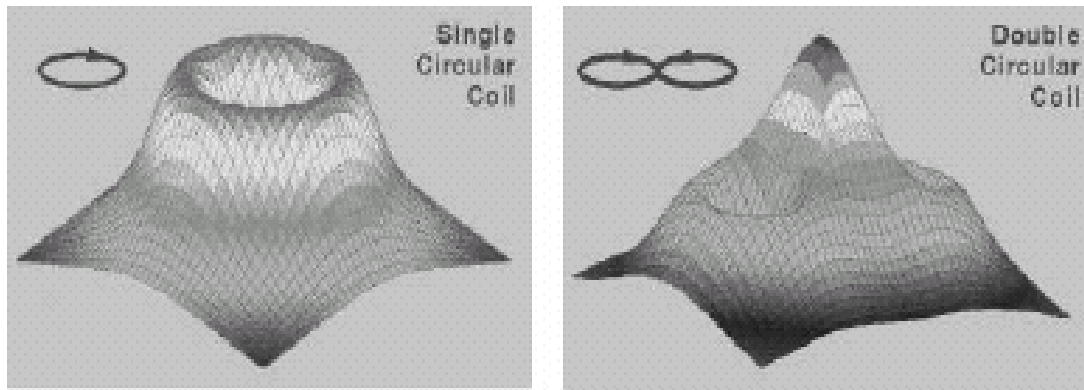


Figure 8: The induced electric field profile of single and double coils differ widely because of their geometry. The induced electric field of a circular coil is zero directly under its centre and reaches maximum approximately under the mean diameter. In the case of double coils it is at a maximum directly under the coil centre and has two smaller characteristic peaks on either side. See Table 1 for winding details.

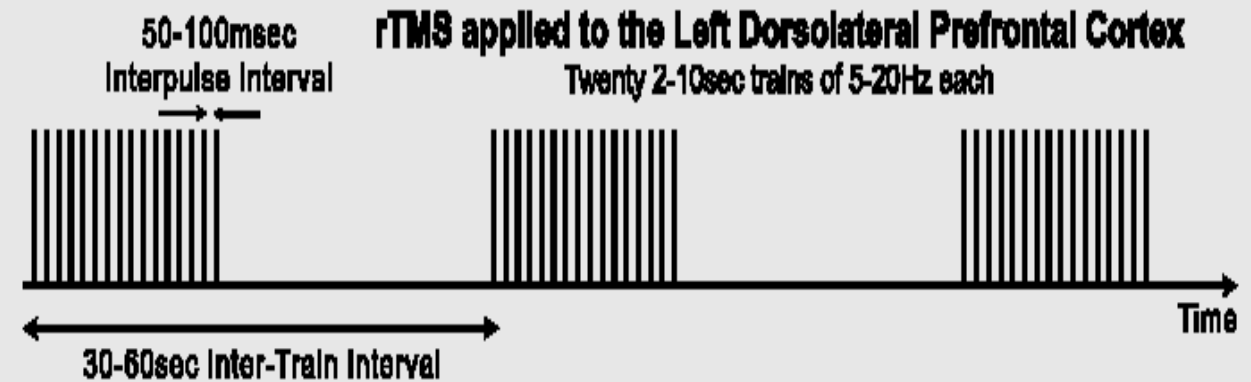


Figure A. Common high frequency rTMS protocols currently applied in the treatment of mood disorders. Brief trains are applied once per minute for twenty minutes. Patient receives ten treatments over a two week period.

Indications and Side Effects of TMS

- Unipolar Depression
- Obsessive Compulsive Disorder
- FDA Approved

- Investigative

- Auditory Hallucinations
- Post Traumatic Stress Disorder
- Generalized Anxiety Disorder
- Tourette Syndrome
- Bipolar Depression
- Autism
- Neurorehabilitation
- Parkinson Disease
- Alzheimer Disease
- Epilepsy
- Focal Dystonia
- Chronic Pain

Side effects

Headache

Pain/discomfort

Nausea

Syncope

Psychiatric sx (?)

Fatigue

Hearing loss

Seizure

Rossi et al,
2009

Clinical Efficacy for MDD

- Initially, many small sample size sham-controlled studies with variability in stimulation parameters, stimulation site, trial duration, etc.
- meta-analyses and recent large multisite trials (Neuronetics¹ n=301 & NIH² n=190) support positive outcomes for rTMS (FDA approved 2008)
- Deep TMS (Brainsway) approved 2013 (pivotal trial with 230 TRD patients)

Clinical Efficacy rTMS for OCD

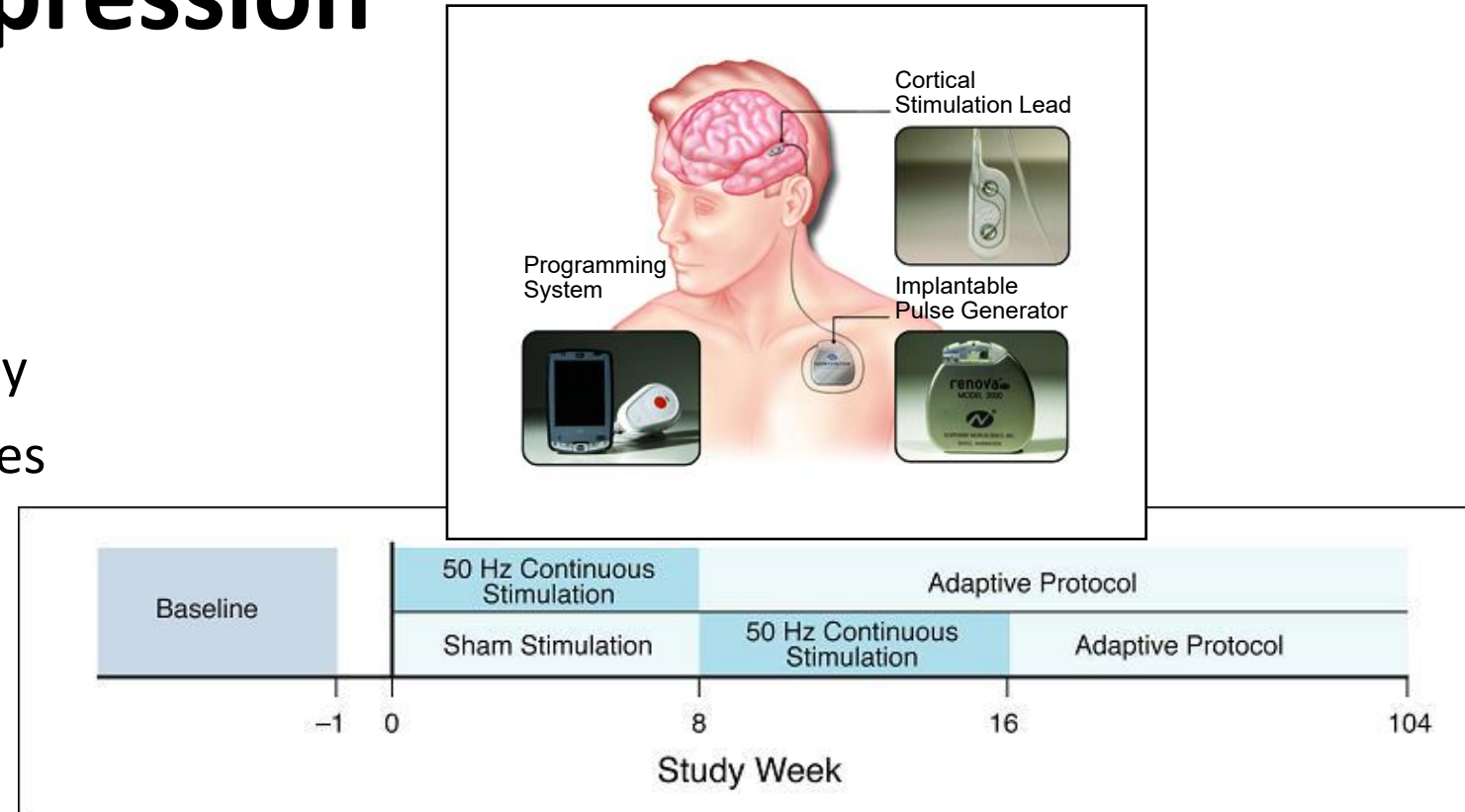
- Multiple rTMS targets for OCD have been explored
- The DLPFC (depression target, approved by FDA for depression) has, generally, not been found to be efficacious for OCD
- Only two controlled trials of standard rTMS for OCD have been positive, each at a different (but similar) target: the dmPFC and pre-SMA

Deep TMS for OCD

- Approved by FDA for OCD in August 2018
- After six weeks of treatment, active > sham ($p=0.0157$)
- 38.1% in active and 11.1% in sham group were responders ($p=0.0033$)
- 54.8% in active and 26.7% in sham were partial responders ($p=0.0459$)

Investigational: Epidural Cortical Stimulation for Treating Major Depression

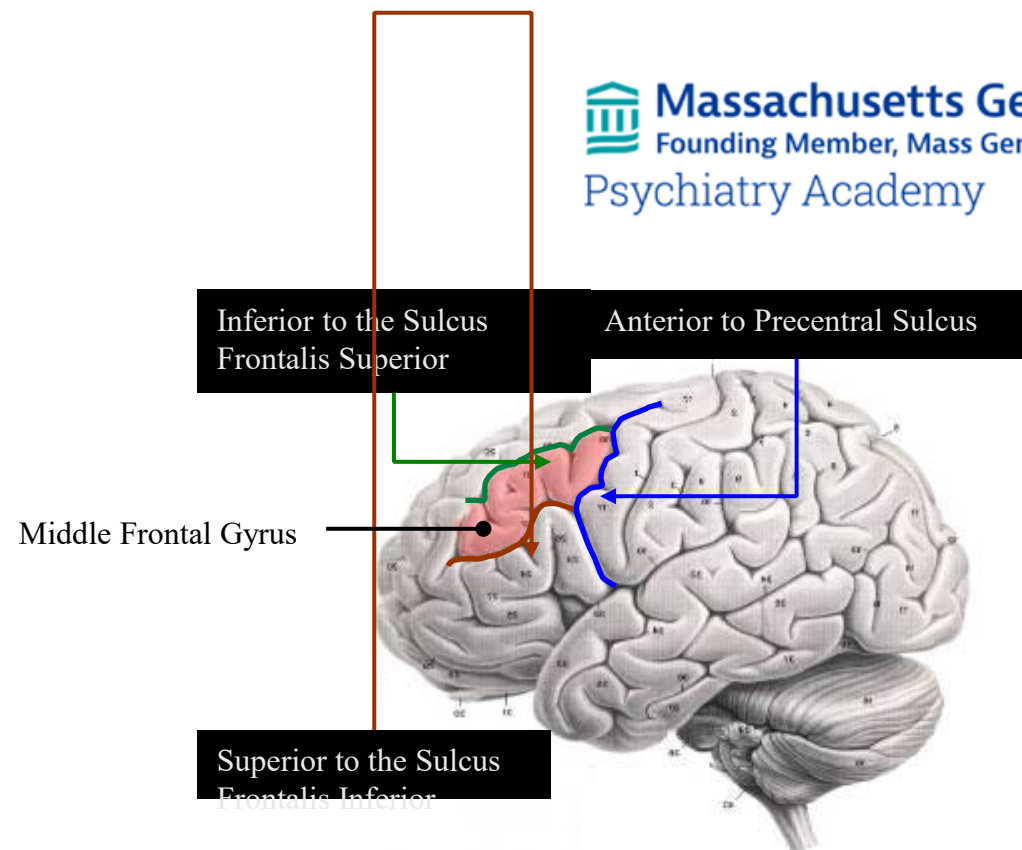
- Multi-center US trial
- 12 subjects
- Single-blinded, sham-controlled
- Assess device and procedure safety
- Assess efficacy via depression scales (HDRS, MADRS) and quality of life measures (GAF, Q-LES-Q)



Kopell BH, Halverson J, Butson CR, Dickinson M, Bobholz J, Harsch H, rainey C, Kondziolka D, Howland R, Eskandar E, Evans KC, Dougherty DD. Epidural cortical stimulation of the left dorsolateral prefrontal cortex for refractory major depressive disorder. *Neurosurgery*. 2011. Nov;69(5):1015-29.

Surgical Target

- Left Hemisphere
- Posterior array 2 cm anterior to precentral sulcus
- Inferior array above inferior frontal sulcus
- Target used in rTMS trials



Included Subjects

Gender	6 female, 6 male
Age (years)	48±6 (39-56)
Years since onset of MDD	27±10 (11-42)
Failed treatments	9.8±1.7 (7-13)
ECT treatments	10 of 12 subjects 16.5±23.2 (0-84)
Duration of current MDE (yrs)	6.9±8.1 (1.3-30)
Baseline HDRS	34.3±5.3 (27.8-46.4)
Baseline MADRS	32.2±4.0 (26.4-40.6)
Baseline GAF	42.0±5.3 (35-50)

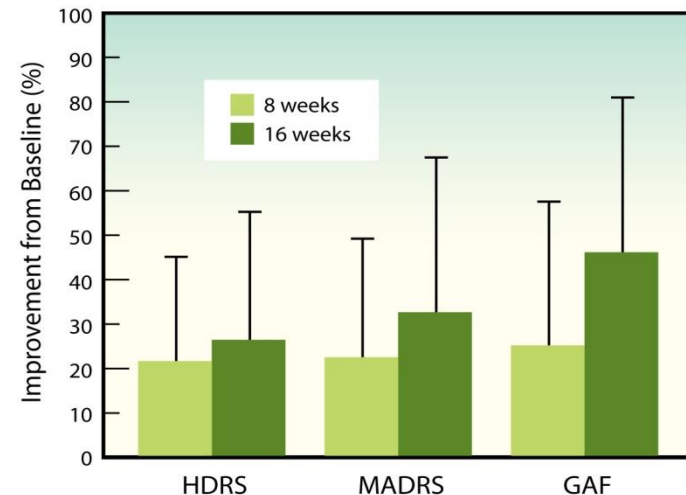
Active Stimulation at 8 and 16 Weeks

Trend: Subjects continue to improve with active cortical stimulation from 8 to 16 Weeks

	Baseline	8 Weeks	16 Weeks
HDRS	34.3±5.0	27.0±8.9 (-21±23%)	25.7±11.0 (-26±29%)
MADRS	32.1±3.8	25.0±9.0 (-22±27%)	21.8±10.9 (-32±35%)
GAF	42.3±5.8	52.3±13.3 (25±32%)	60.1±13.0 (46±34%)

* 16-wk time point for sham stimulation patients,
8-wk time point for active stimulation patients

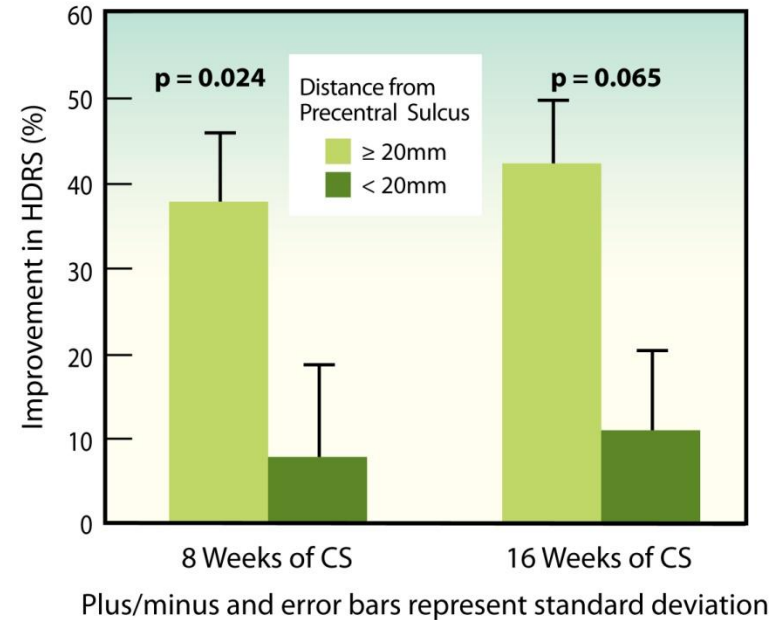
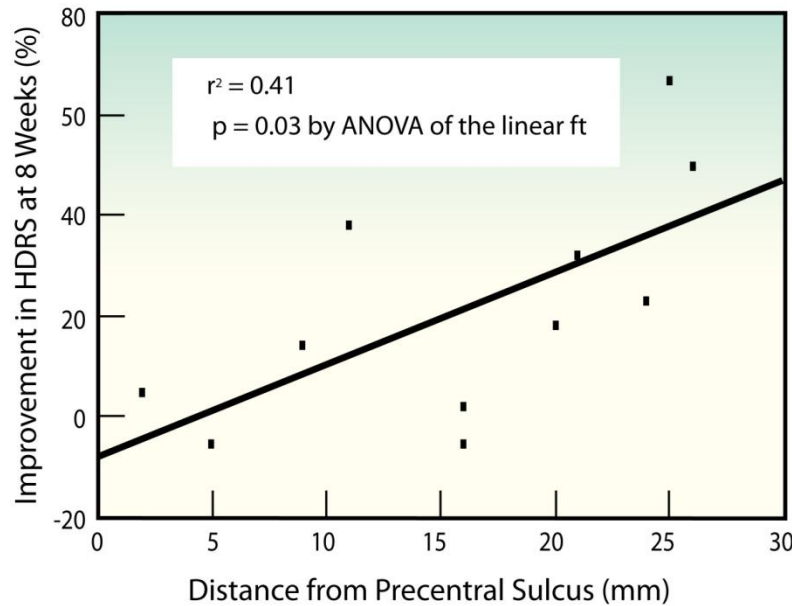
** 24-wk time point for sham stimulation patients,
16-wk time point for active stimulation patients



Plus/minus and error bars represent standard deviation

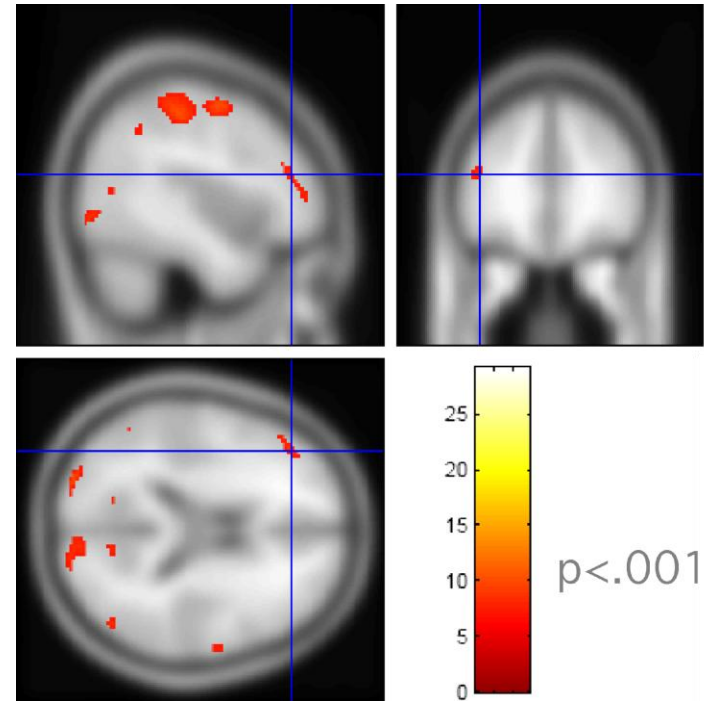
All p -values > 0.5

Electrode Location Influences Outcome



Baseline Metabolic Activity Predicts Patient Response

- Baseline FDG-PET acquired prior to implantation
- Magnitude of decreased metabolism at left DLPFC correlates with magnitude of improvement with active stimulation ($p < .001$)¹
- Potential exists for improving the subject selection process



Kopell BH, Halverson J, Butson CR, Dickinson M, Bobholz J, Harsch H, rainey C, Kondziolka D, Howland R, Eskandar E, Evans KC, Dougherty DD. Epidural cortical stimulation of the left dorsolateral prefrontal cortex for refractory major depressive disorder. *Neurosurgery*. 2011. Nov;69(5):1015-29.

Ablative Limbic System Surgery

Prior Treatment Criteria

- Required
 - Multiple serial adequate trials of antidepressants of all classes
 - Adequate trial of multiple serial augmentation strategies
 - Adequate trials of alternative therapies (TMS, ketamine)
 - Adequate trial of psychotherapy (especially CBT)
 - Adequate trial of ECT

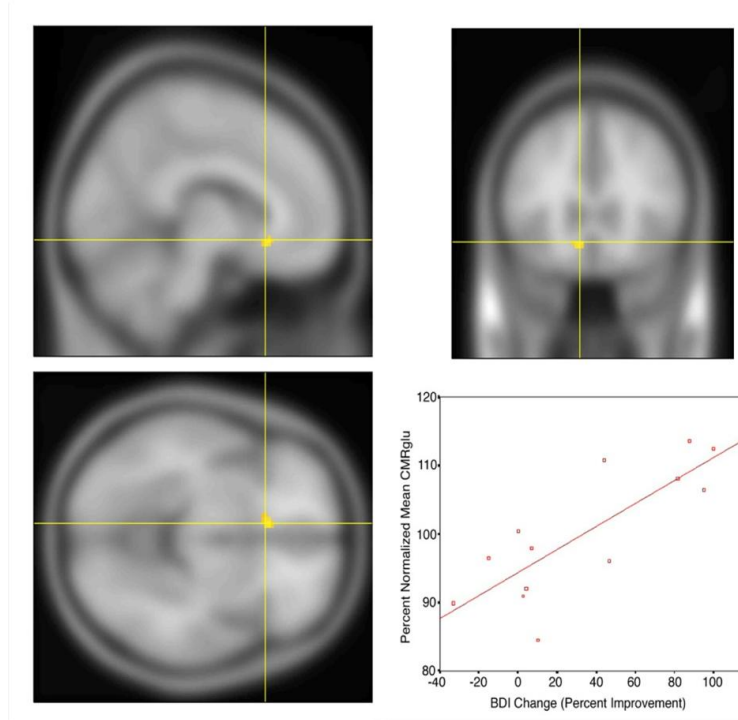
Effectiveness of Cingulotomy for MDD

- 33 patients undergoing anterior cingulotomy
- At mean f/u of 30 months, 12 (36%) were responders and 12 (39%) were partial responders
- approximately 75% received some benefit
- Minimal adverse events

Shields DC, Asaad W, Eskandar EN, Jain FA, Cosgrove GR, Flaherty AW, Cassem EH, Price BH, Rauch SL, Dougherty DD. Prospective assessment of stereotactic ablative surgery for intractable major depression. *Biol Psychiatry*. 2008 Sep;15;64(6):449-54. Epub 2008 May 16.

Baseline Subgenual PFC Metabolism Predicts Subsequent Response to Anterior Cingulotomy for Major Depression

Fig. 1



Dougherty DD, Weiss AP, Cosgrove GR, Alpert NM, Cassem EH, Nierenberg AA, Price BH, Mayberg HS, Fischman AJ, Rauch SL. Cerebral metabolic correlates as potential predictors of response to anterior cingulotomy for major depression. *J Neurosurg*. 2003;99:1010-1017.

Effectiveness of Cingulotomy for OCD

- Total n =64; mean f/u = 63.8 months
- Full response (35%+ YBOCS improvement) = 47%
- Partial response (25-34% YBOCS improvement) = 22%
- Minimal adverse events

Sheth SA, Neal J, Frances Tangherlini F, Mian MK, Andre Gentil A, Cosgrove GR, Eskandar EN, Dougherty DD.
Cingulotomy for treatment-refractory obsessive-compulsive disorder: A prospective long-term follow-up of 64 patients.
J Neurosurg. 2012 Dec 14. [Epub ahead of print]

Deep Brain Stimulation

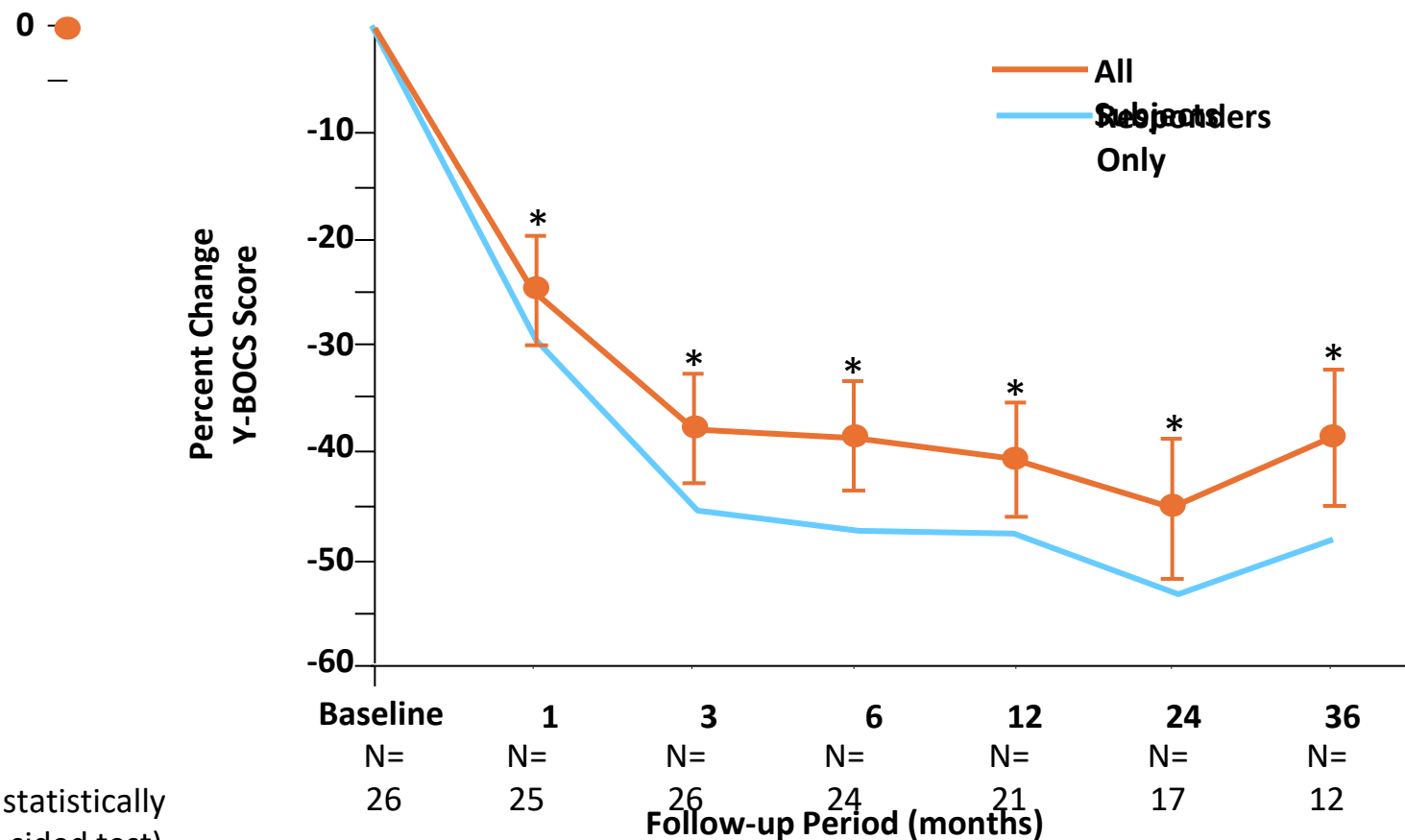
DBS Patient Demographics*

	Mean (years)	Minimum (years)	Maximum (years)
Age at Implantation	37.1	22.0	59.0
Age at OCD Onset	15.1	7.0	34.0
Symptom Duration	22.0	8.0	41.0
Gender	M = 53.8% F = 46.2%		
History of Depression	Yes = 88.5% No = 11.5%		

* Reclaim DBS Therapy for OCD – Lead Kit for Deep Brain Stimulation Implant Manual; part number MA10549A002.

Y-BOCS Scale

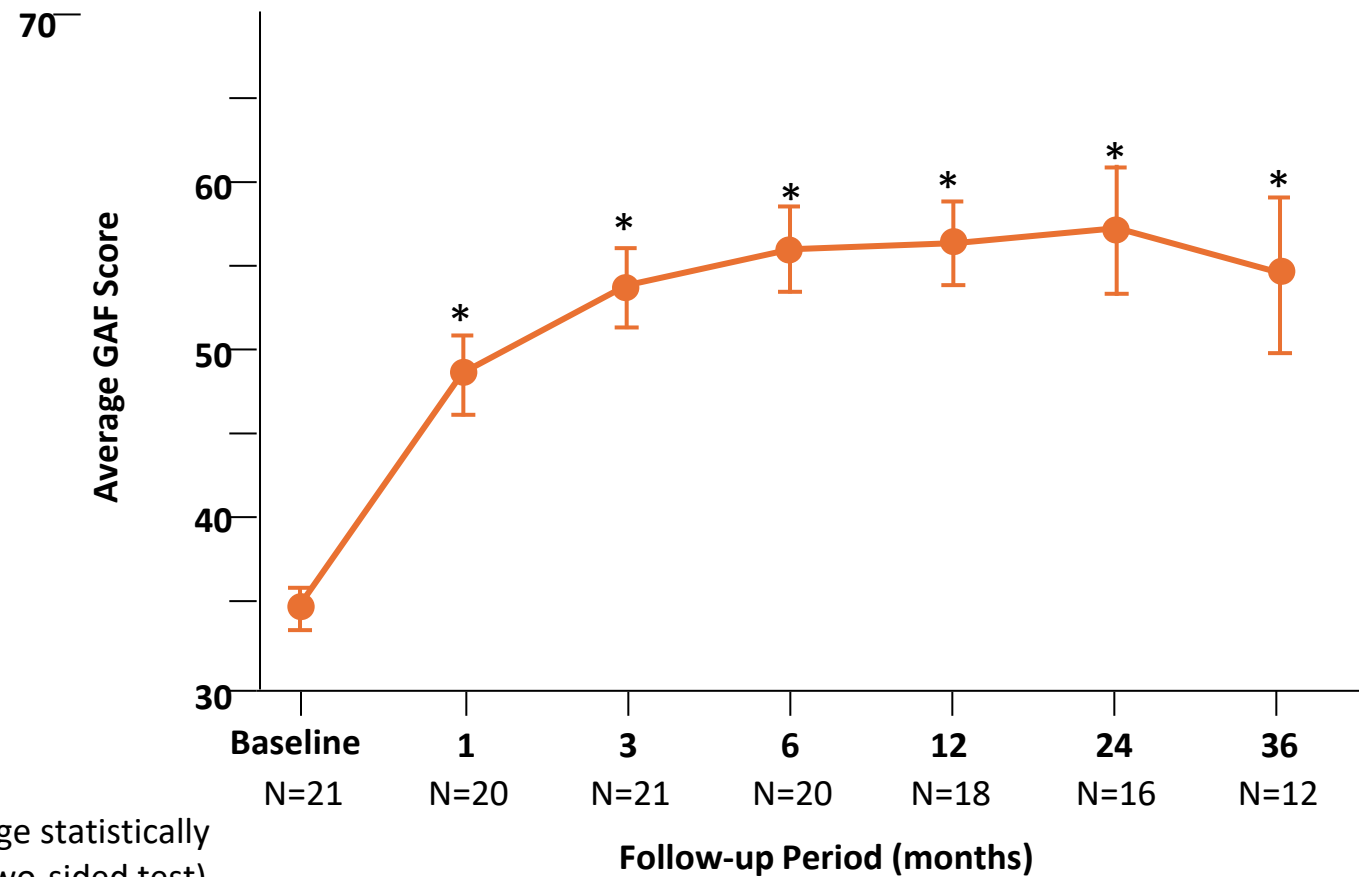
Percent of Improvement with DBS Follow-up Study Results



* Within-subject change statistically significant ($p \leq .001$, two-sided test).

GAF Scale

Improvement in Score with DBS Follow-up Study Results



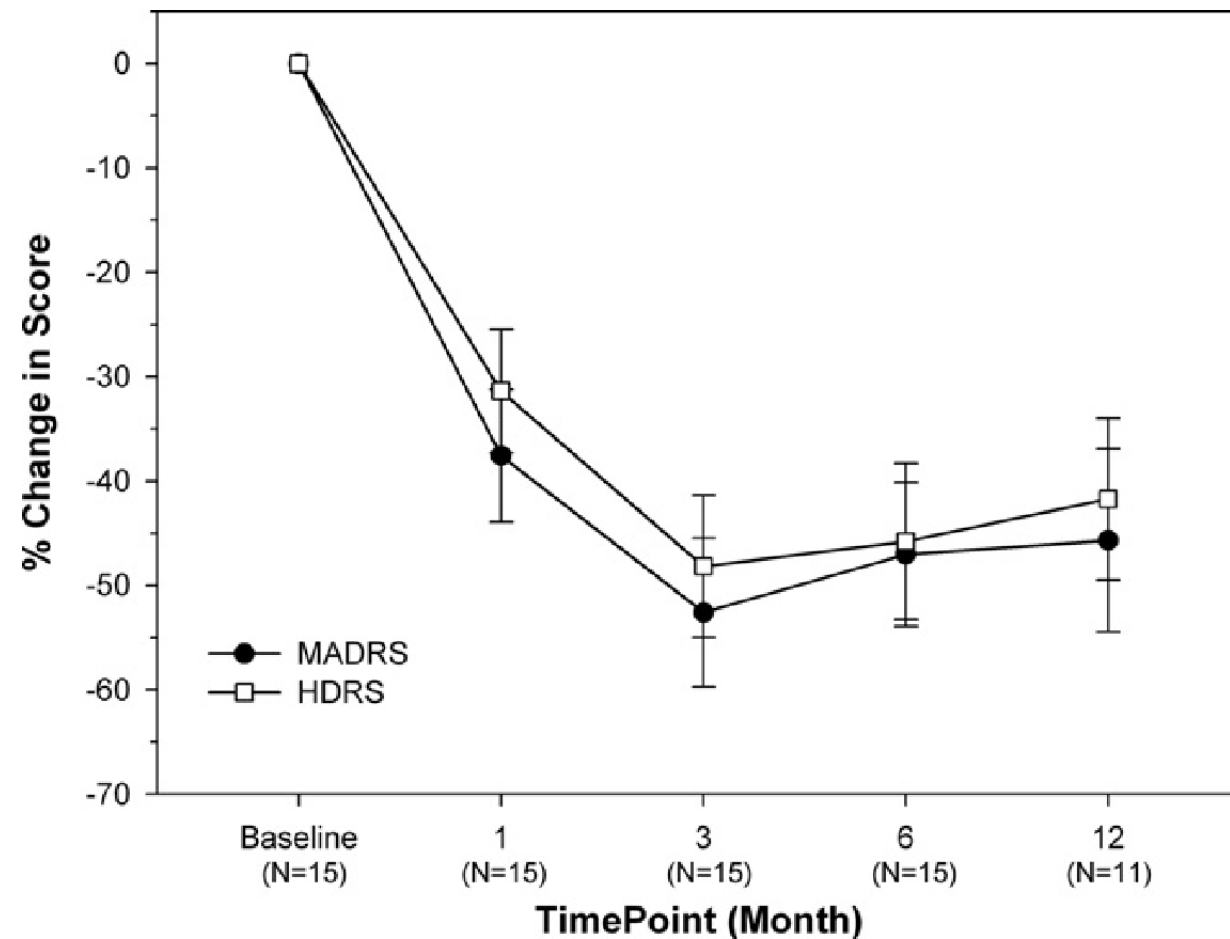
* Within-subject change statistically significant ($p \leq .001$, two-sided test).

VC/VS DBS for OCD

- Approved by FDA under the HDE mechanism in 2009
- Reimbursed by third party payers
- Requires visits every 2 weeks for the first 3 months, less frequently afterwards
- Batteries last 5-7 years or rechargeables

VC/VS for MDD

- 15 subjects from MGH, Brown University, and Cleveland Clinic with treatment resistant depression
- Similar inclusion/exclusion as cortical stimulation and anterior cingulotomy
- Mean baseline MADRS was 34.8 (7.3)
- Device implantation followed by stimulation two weeks later
- Primary outcome measure was MADRS



Malone DA Jr*, Dougherty DD*, Rezai AR, Carpenter LL, Friehts GM, Eskandar EN, Rauch SL, Rasmussen SA, Machado AG, Kubu CS, Tyrka AR, Price LH, Stypulkowski PH, Giftakis JE, Rise MT, Malloy PF, Salloway SP, Greenberg BD. Deep brain stimulation of the ventral capsule/ventral striatum

for treatment-resistant depression. *Biol Psychiatry*. 2009 Feb 15;65(4):267-75. Epub 2008 Oct 8.

Results

- 8/15 subjects experienced at least a 50% reduction of MADRS scores at 3 months follow-up
- 5/15 subjects experienced remission (MADRS score of 10 or less) at 3 months follow-up
- Adverse events included two instances of worsening depression (device inadvertently turned off) and one instance of hypomania (resolved with reduction of stimulation parameters)

However...

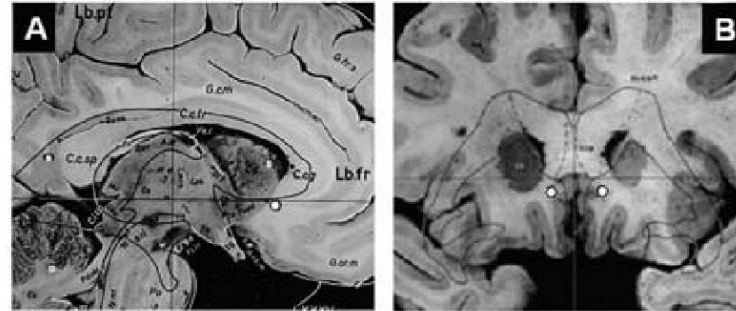
- Large, multisite randomized controlled trial for potential FDA approval...

NEGATIVE!!

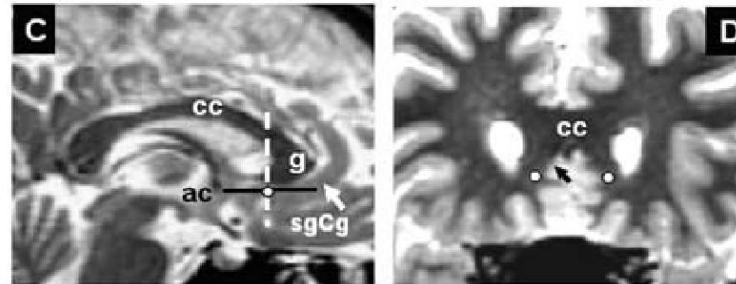
- New trial sponsored by Abbott – recruiting very large N, site of implant at the Subcingulate area 25, personalized through tractography

DBS: Subgenual Cingulate (Cg25) Region

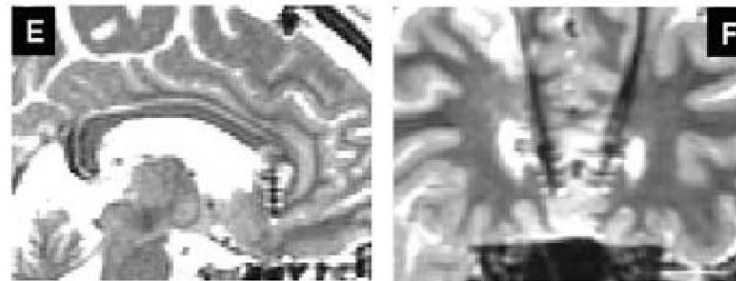
Atlas
Target



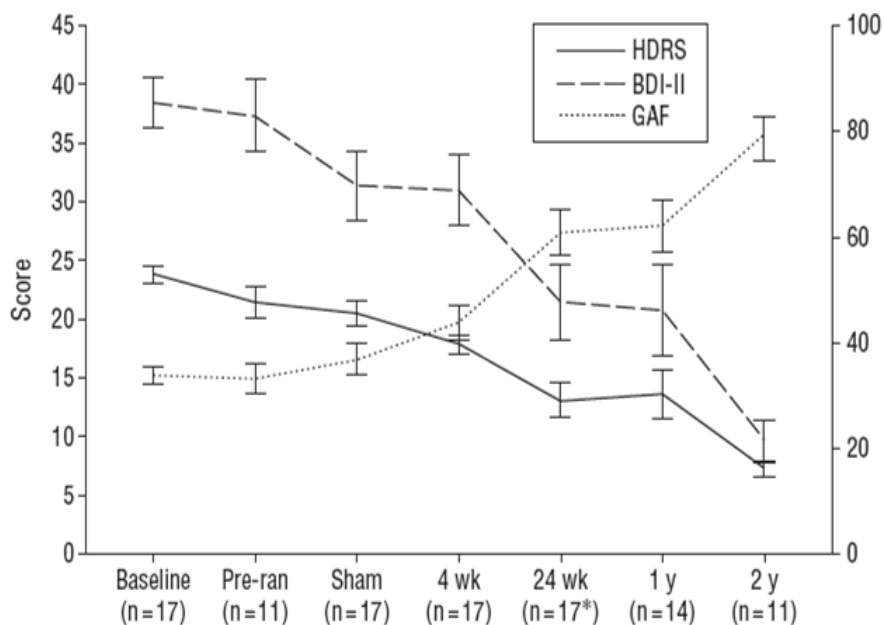
Pre-op MRI
Target
Localization



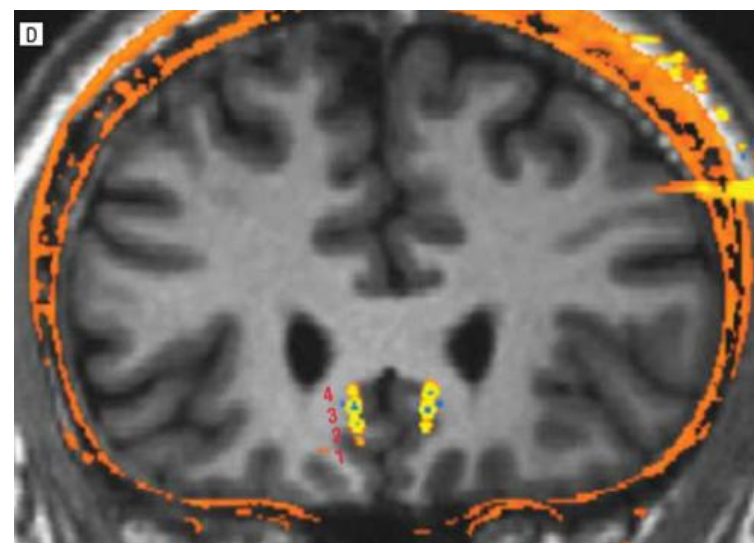
Post-op MRI
Electrode
Location



DBS of Subcallosal Cingulate



10 MDD, 7 Bipolar
Single-blind
sham 4-weeks lead-in
24 weeks active
discontinuation (N=3)



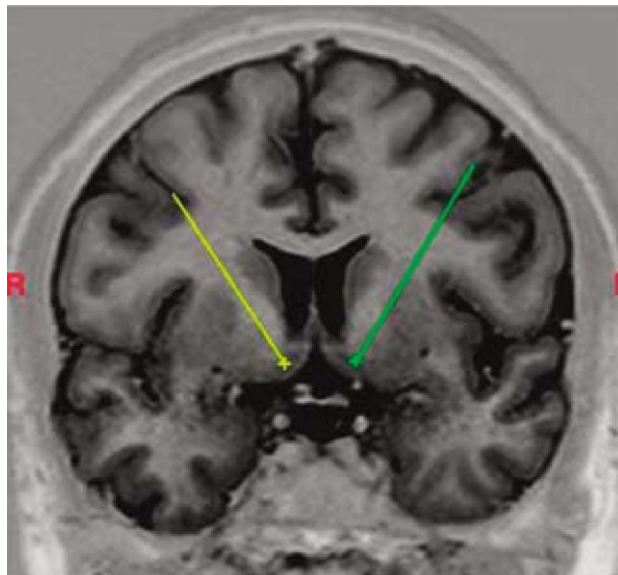
18% Remission and 41% Response @ 24 weeks
36% Remission and 36% Response after 1 year
58% Remission and 92% Response after 2 years

This information concerns a use that has not been approved by the US Food and Drug Administration.

Holtzheimer, et al. *Arch Gen Psychiatry*. Published online January 2, 2012.

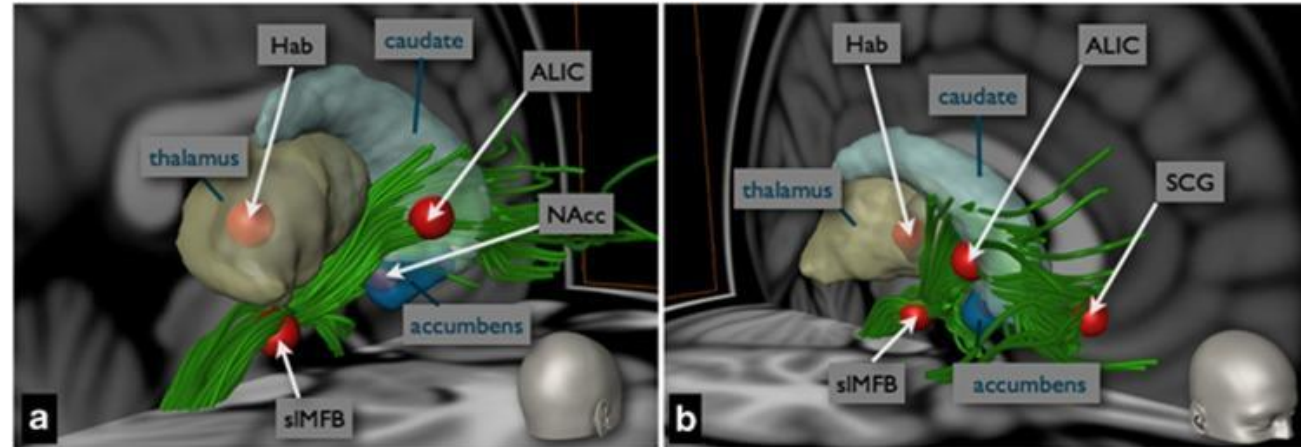
Nucleus Accumbens Target

- At 12 month f/u, 5 of 10 TRD pts achieved at least 50% reduction of HDRS
- No controlled trials to date



Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, Axmacher N, Lemke M, Cooper-Mahkorn D, Cohen MX, Brockmann H, Lenartz D, Sturm V, Schlaepfer TE. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol Psychiatry*. 2010 Jan 15;67(2):110-6.

Medial Forebrain Bundle

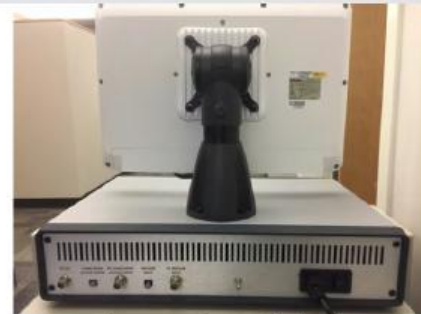


- Six of seven TRD patients met criteria for response after only 7 days of stimulation
- Initial proof of concept
- No controlled trials to date

Investigational: Transcranial Focused Ultrasound/Low Intensity Focused Ultrasound Pulsation (tFUS/LIFUP)



Ultrasound Console (front)



Ultrasound Console (rear)



Transducer showing clip mechanism



Transducer Holder

Brainsonix BX Pulsar 1002

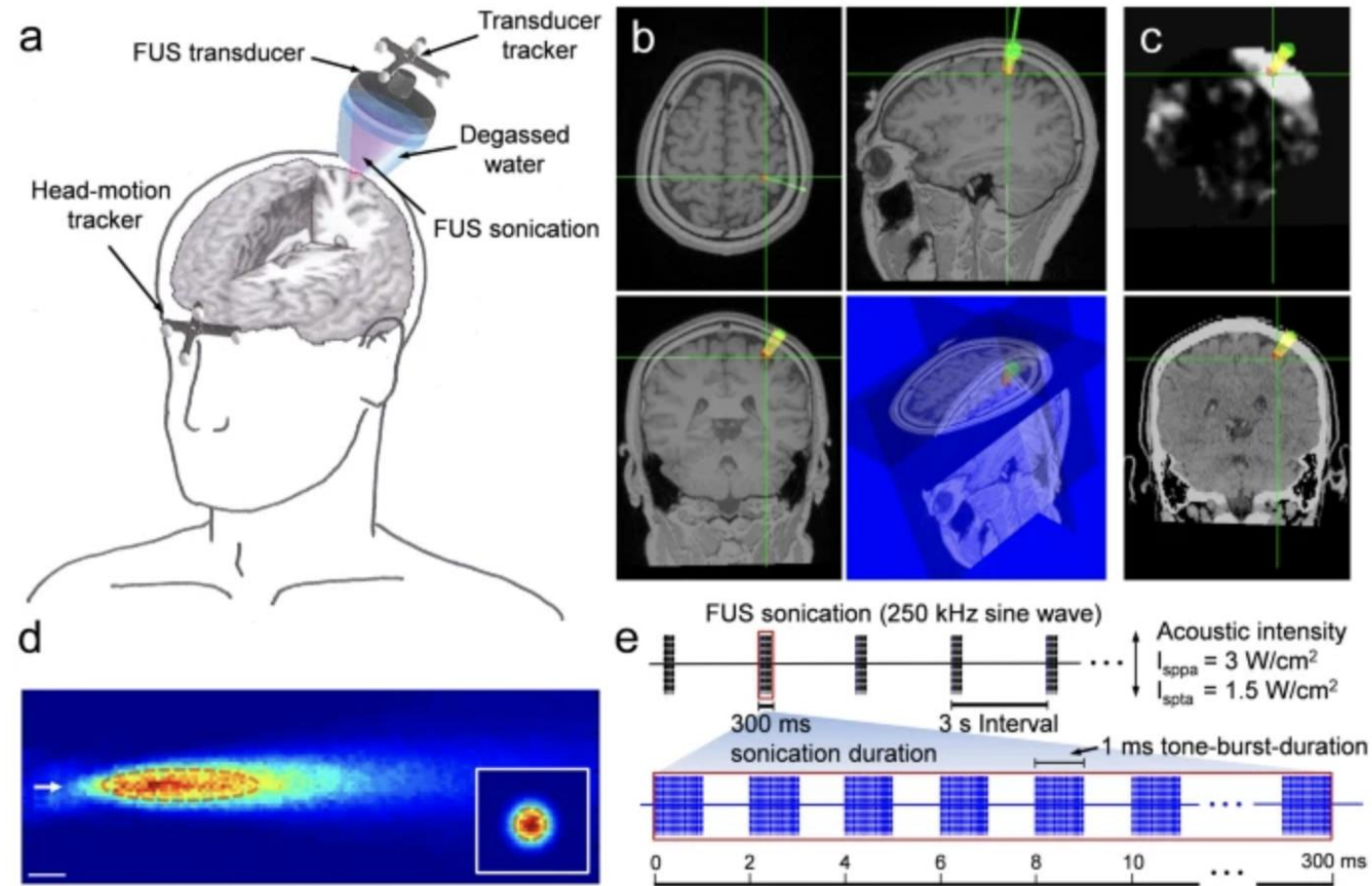


Coupling pad attached to transducer



Transducer and Holder strapped to subject

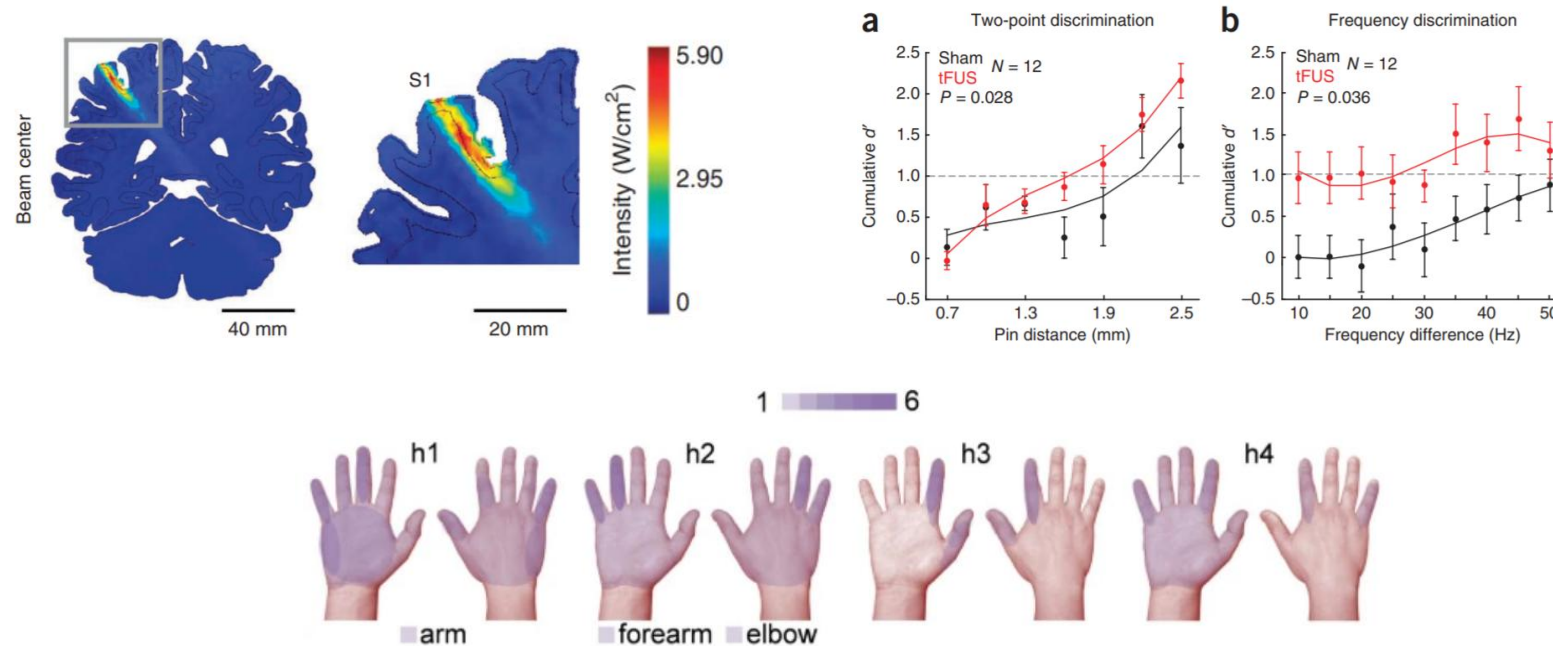
Focused ultrasound (FUS)



Schematic of the image-guided FUS sonication setup and parameters.

Early Studies

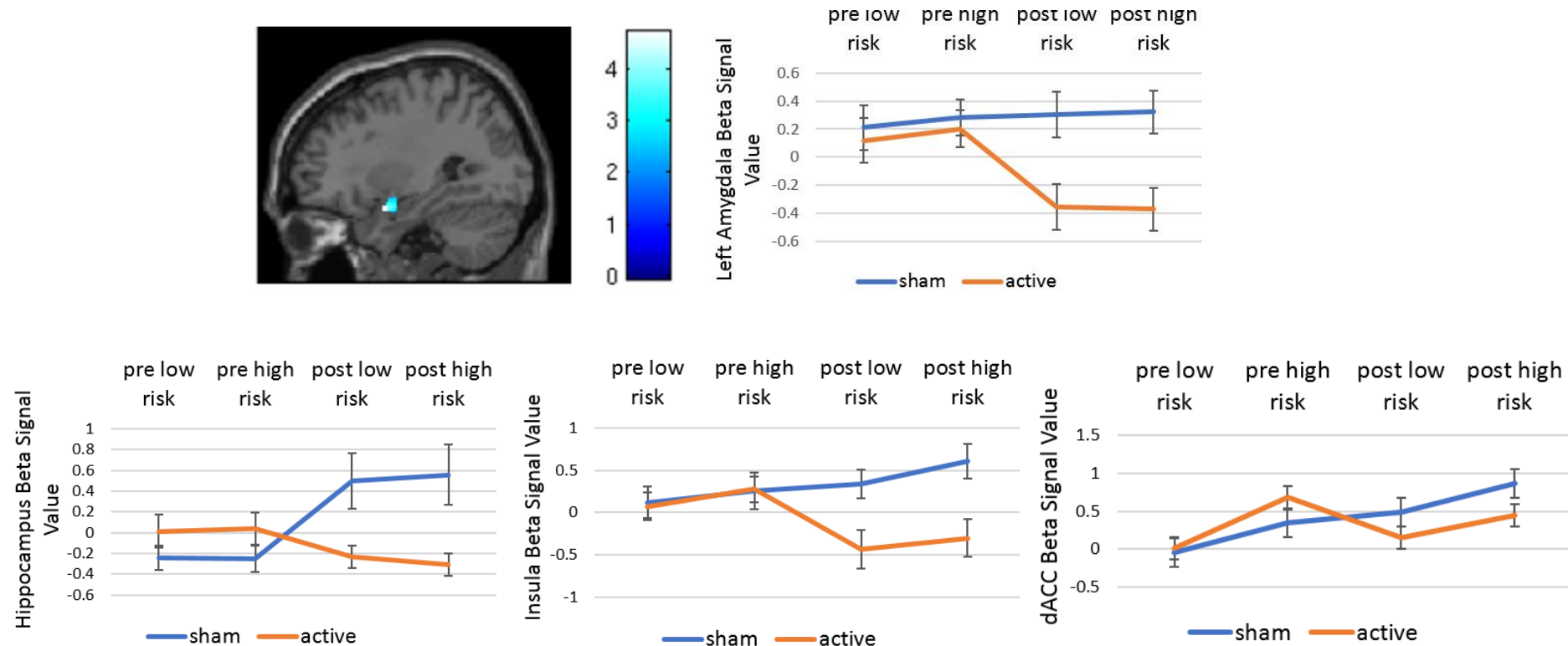
tFUS of the somatosensory cortex can elicit tactile sensations and enhance sensory detection



Legon, et al. *Nature Neuroscience*. 2014.

Lee, et al. *Scientific Reports*. 2015.

tFUS of the Amygdala: Task fMRI



In practice:

ECT. -MDD, BP, SKZ

Controlled seizure
Hospital setting
Covered by insurance
x3/week, 2-3 weeks
General anesthesia
Memory side effects

TMS -MDD, OCD

No seizure
Covered by insurance
Daily, 5 weeks
No anesthesia
No memory side effects

VNS - MDD

Surgery and implanted device
Covered 35% cases by private payers insurance
Visits for few months (programming)
Battery replacement
No memory side effects

DBS - OCD

Surgery

Covered by insurance under HDE
Programming visit, battery replacement



Research only

DBS for MDD

LiFU - cortic stim

Collaborators

Massachusetts General Hospital

Psychiatric Neurosurgery Committee

Joan Camprodon, Mark Richardson

Alice Flaherty, Sahand BabapoorFarrokhan

Center for Morphometric Analysis

Nikos Makris, David Kennedy,

Verne Caviness

PET Laboratory

Tom Brady, Alan Fischman, Nat Alpert

Butler Hospital Site

Ben Greenberg,

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University of Florida Site

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