MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Stimulation and/or Surgical Approaches to Psychiatric Illness

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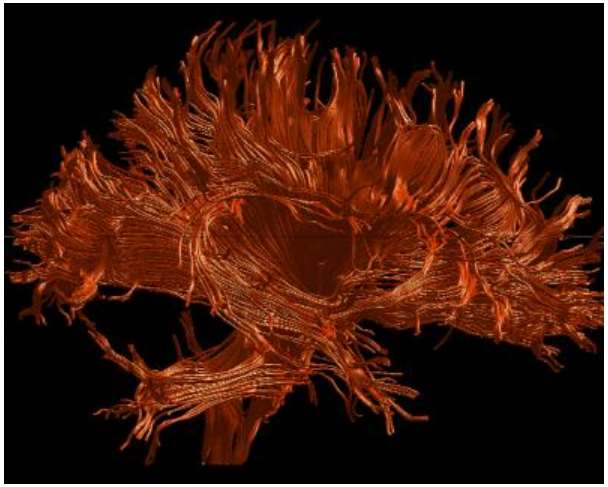
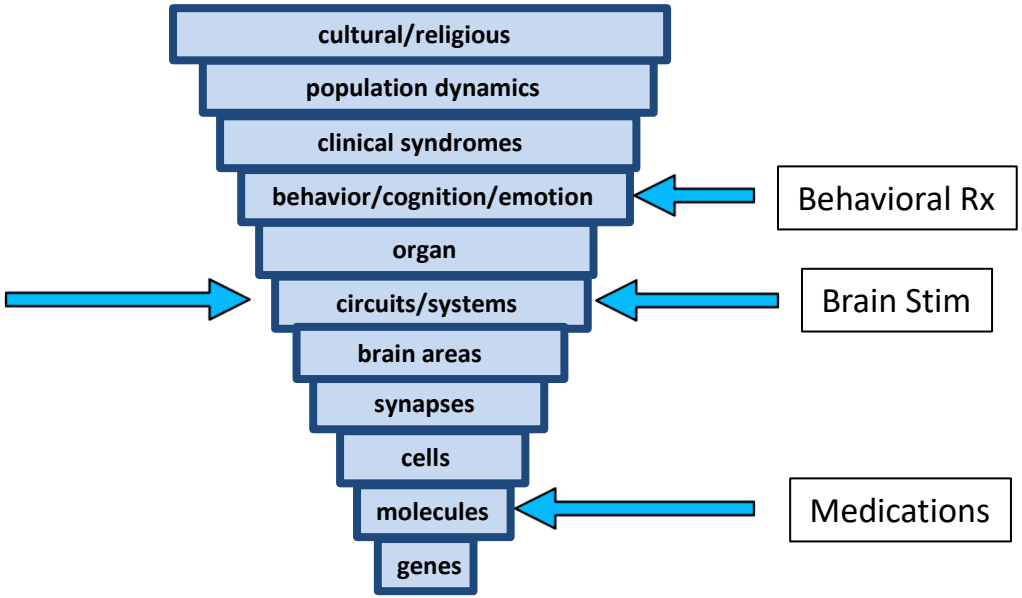
Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

- Funding: NIMH, NIDA, NIAAA, NIA, NIH Brain Initiative, PCORI, Harvard Players Health Study, Harvard Brain Initiative, Gerstner Foundation, AE Foundation, Solinsky Foundation.
- Scientific Advisory Board: Feelmore Labs, Hyka Therapeutics
- Consultant: Neuronetics

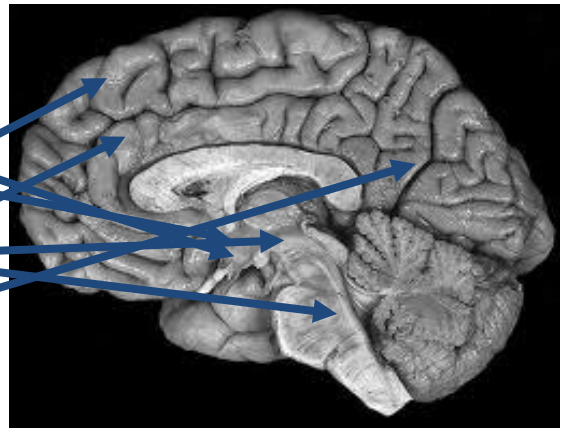
Neuropsychiatry: Disorders of Connectivity





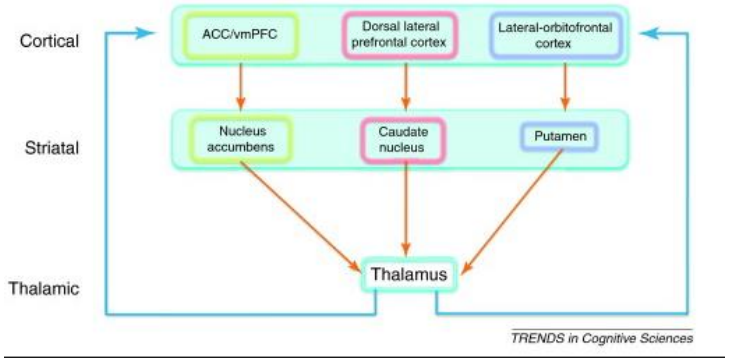
Circuits and Dimensions

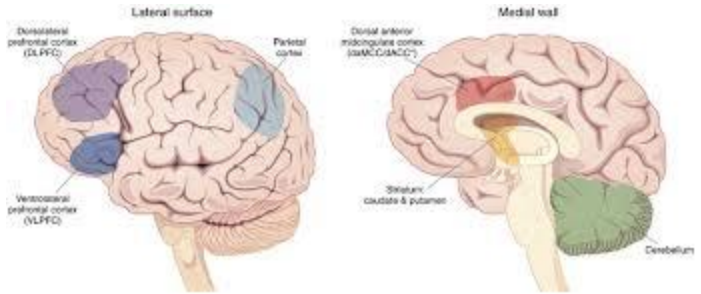
- Depressed mood
- Motivation/Drive
- Energy
- Sleep/Appetite
- Cognition/Attention
- Rumination/Guilt
- Self-Harm



Clinical/Behavioral dimensions shared by different syndromes!

Beyond Mood





Bush, 2010

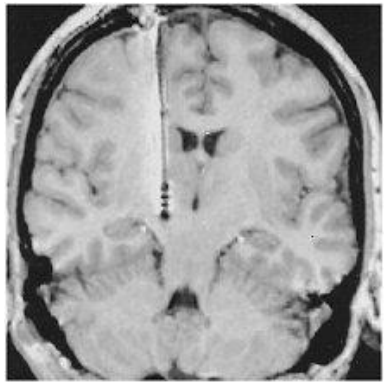
Brain Stimulation - Neuromodulation

Invasive

Deep Brain Stimulation (DBS)

Vagal Nerve Stimulation (VNS)

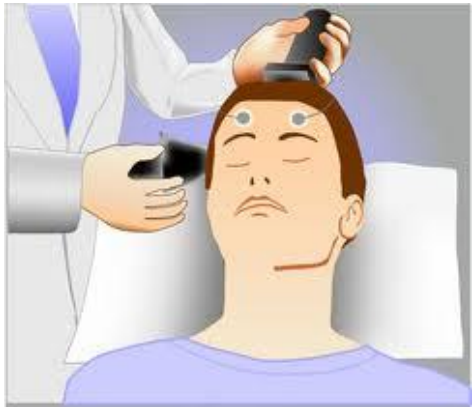
Epidural Stimulation (ES)



Convulsive

Electroconvulsive Therapy (ECT)

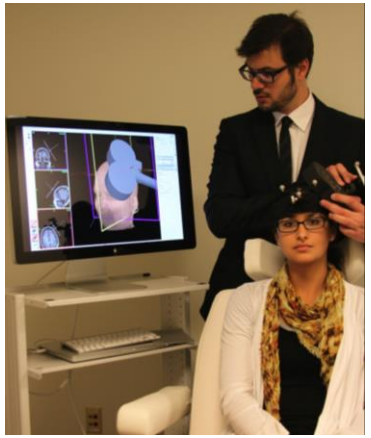
Magnetic Seizure Therapy (MST)



Noninvasive

Transcranial Magnetic Stimulation (TMS)

Transcranial Direct Current Stimulation (tDCS)

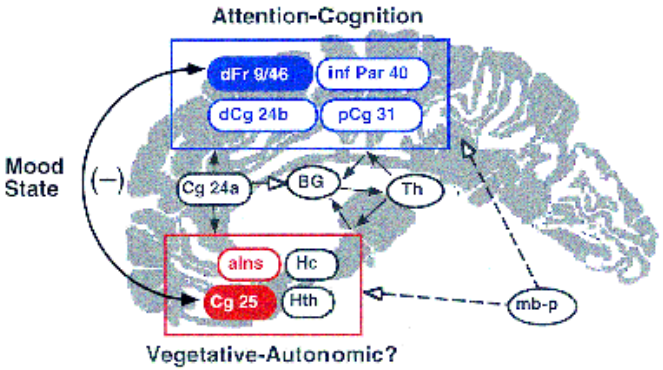


(Therapeutic) Neuromodulation and the FDA

DEVICE	CONDITION	FDA STATUS
Deep Brain Stimulation	Chronic Pain	First indication, now revoked
	Parkinson´s Disease	General Approval
	Essential Tremor	General Approval
	Dystonia	Humanitarian Device Exception
	Obsessive Compulsive Disorder	Humanitarian Device Exception
	Major Depressive Disorder	Experimental
Vagus Nerve Stimulation	Epilepsy	General Approval
	Major Depressive Disorder	General Approval
Transcranial Magnetic Stimulation	Major Depressive Disorder	General Approval
	Migraines: acute management	General Approval
	Obsessive Compulsive Disorder	General Approval
	Smoking Cessation	General Approval
Transcranial Current Stimulation	MDD, ADHD, Alzheimer, Epilepsy…	Experimental

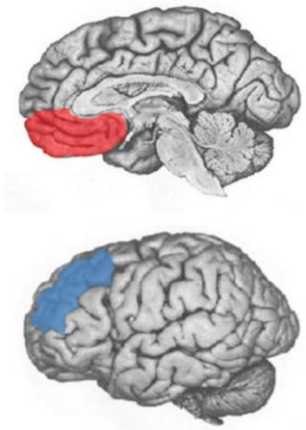
Neuromodulation: Need to know…

The circuit(s)



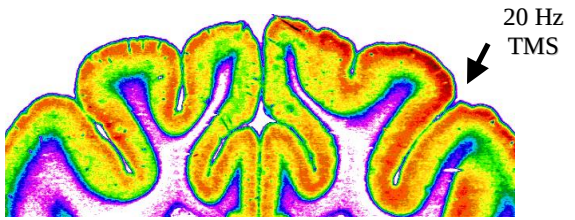
Mayberg et al., 2010

The target(s)



Koenigs et al. 2009

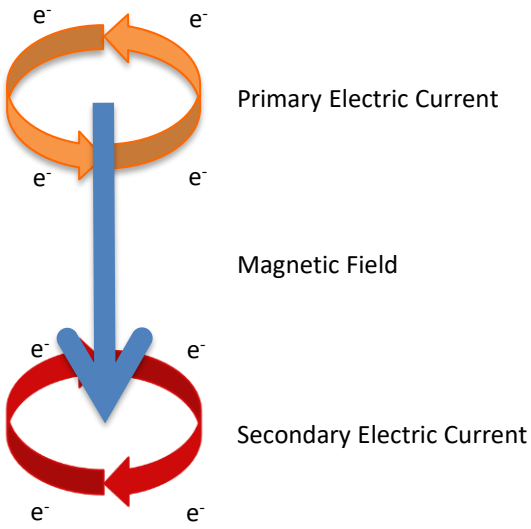
Direction of modulation



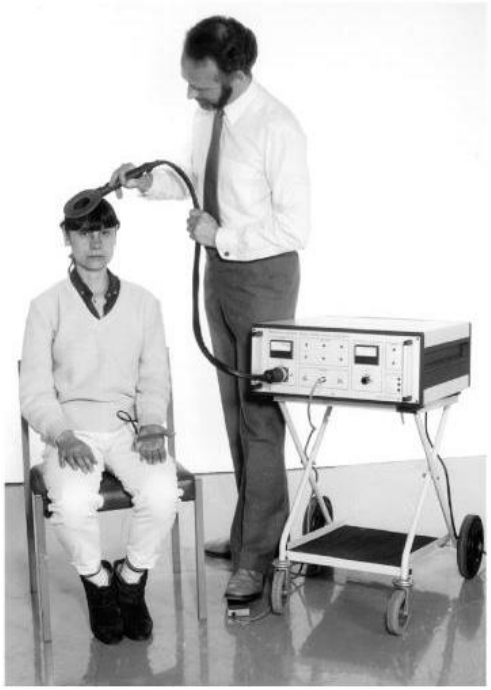
Valero Cabre et al., 2008

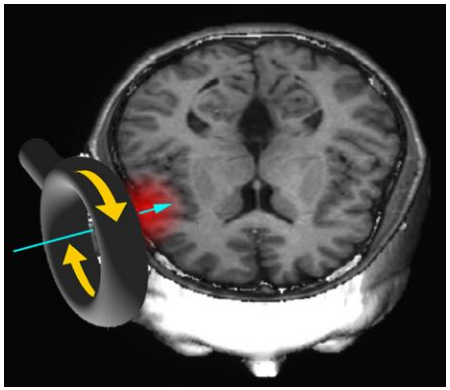
Transcranial Magnetic Stimulation

1831 Faraday's Electromagnetic Induction



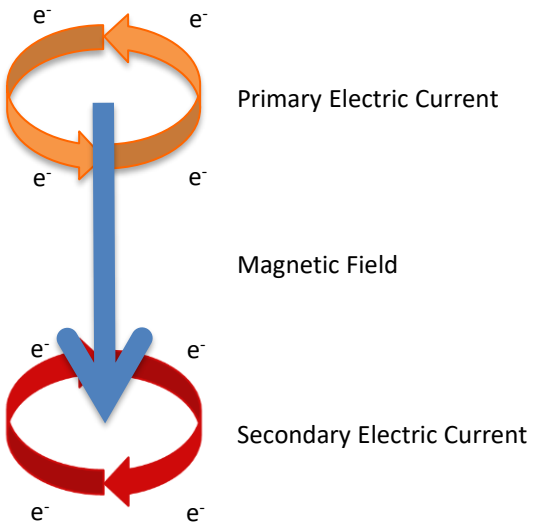
Anthony Barker 1984



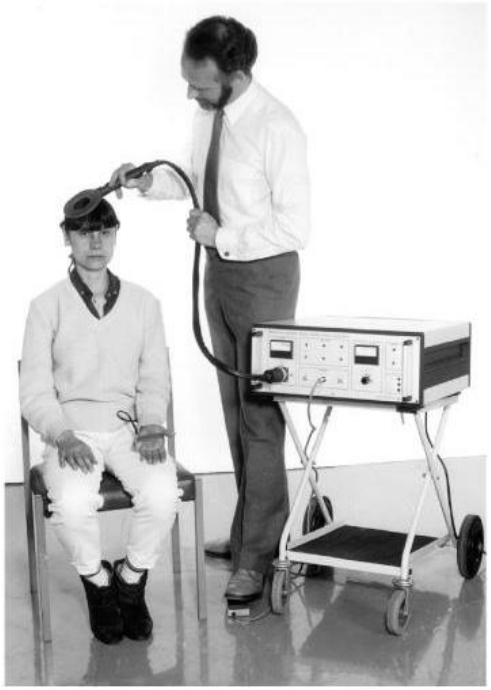


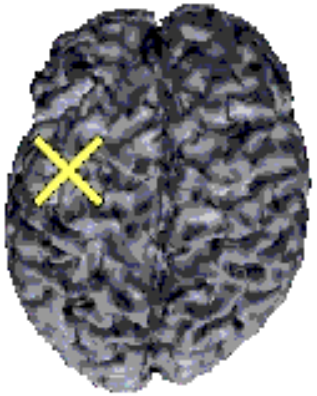
Transcranial Magnetic Stimulation

1831 Faraday's Electromagnetic Induction

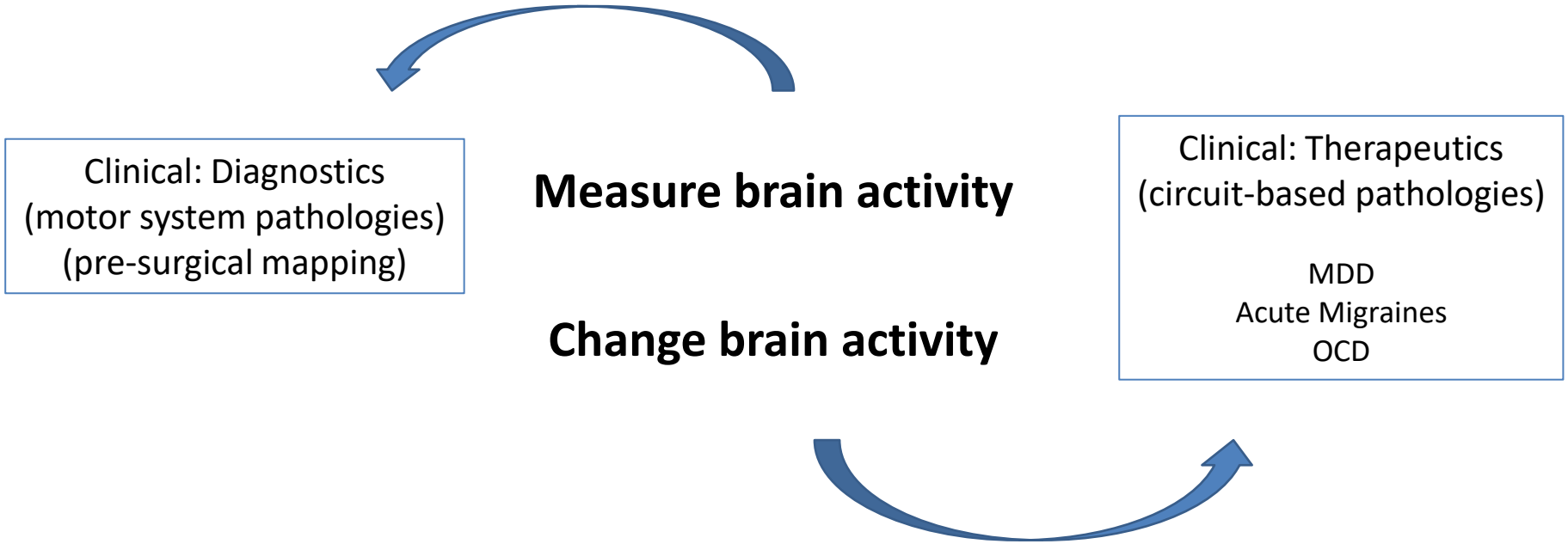


Anthony Barker 1984





TMS Applications



Relevant Parameters

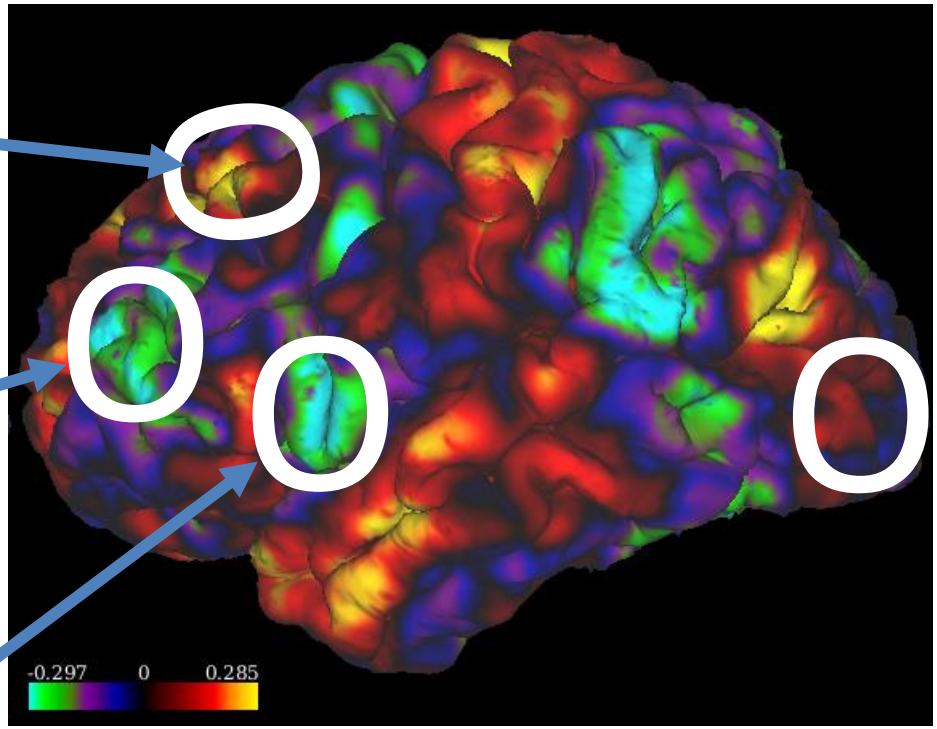
1) Location (low tech vs. neuronavigation)
2) Focality & Depth (coil selection)
3) Frequency (up- or downregulate)
4) Intensity (relative to stimulator or subject)
5) Duration (number of pulses / sessions)

Therapeutic Targets

OCD Target:
DMPFC/pre-SMA

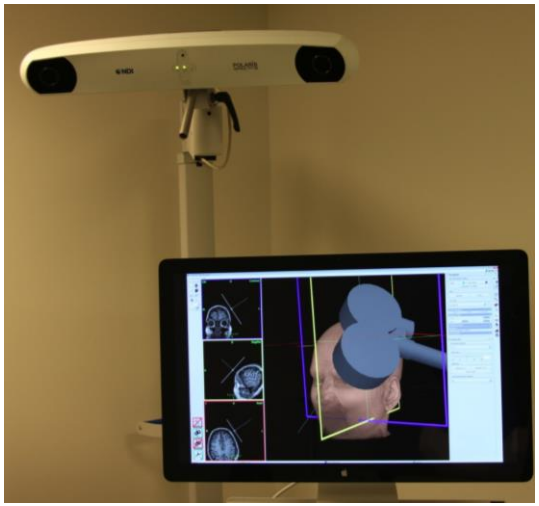
MDD Target:
DLPFC

Smoking Cessation:
VLPFC/Insula

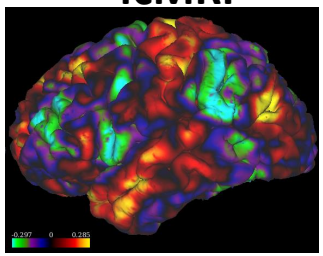


Migraine Target:
Occipital pole

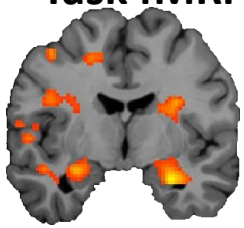
Localization: Neuronavigation



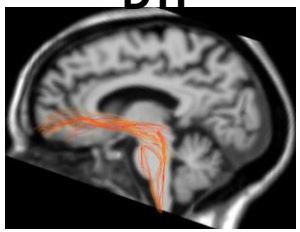
fcMRI

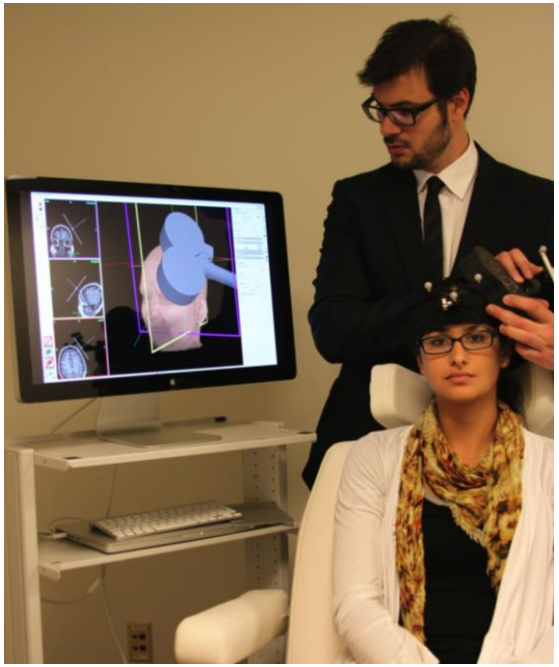


Task fMRI

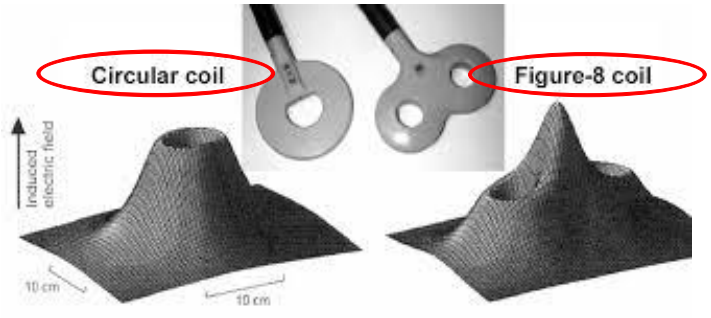


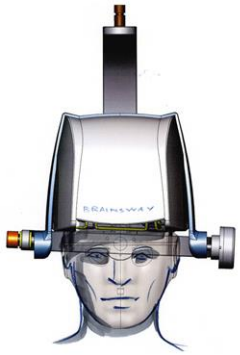
DTI





Depth & Focality : TMS Coils





Chosen design concept

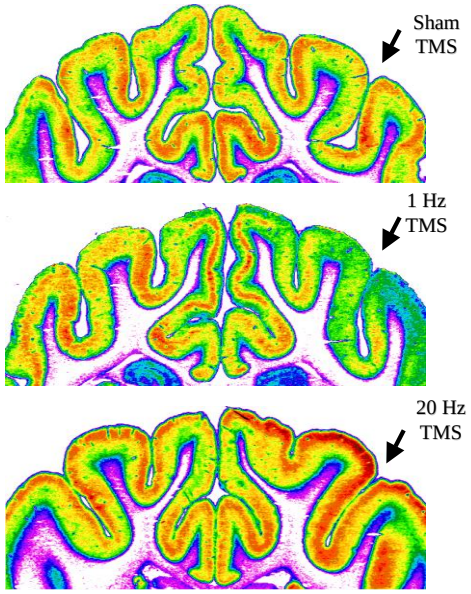
H-coil

Frequency: Neuromodulation with rTMS

Frequency-Dependent Effects

Repetitive Stimulation (rTMS):

- Low frequency 1Hz --> decrease activity (LTD-like)
- High frequency 5-20Hz --> increase activity (LTP-like)
- New Protocols: Theta Burst Stimulation (TBS)
  - Continuous TBS (cTBS) --> decrease activity (LTD-like)
  - Intermittent TBS (iTBS) --> increase activity (LTP-like)



Metabolic changes (2-deoxyglucose uptake) in the cortex of the cat after rTMS (Valero-Cabré et al.)

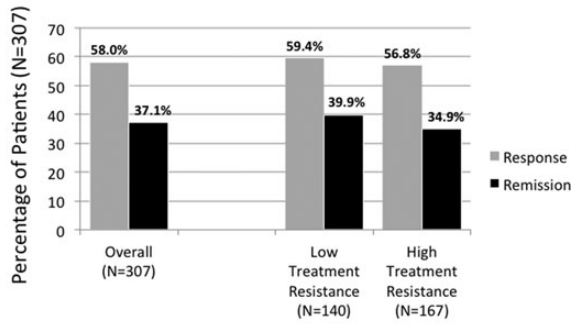
TMS “dose”

- Pulse Intensity
  - Magnetic Field Intensity (Tesla)
  - % of maximum stimulator output
  - Percentage of MT (individualized dosing)
  - Pulse intensity affects depth and focality
- Number of Pulses (duration of session)
- Number of Sessions

- Dose matters! Less variability and greater effect sizes

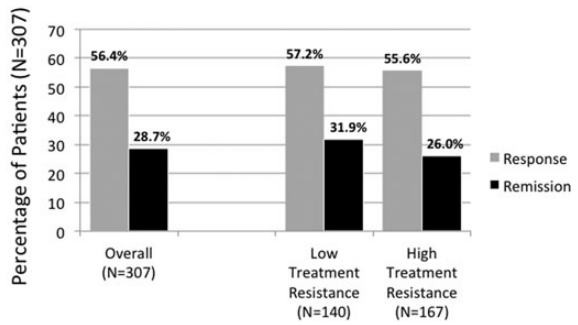
Effectiveness Naturalistic Studies in MDD

CGI-S Outcomes



LOCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

PHQ-9 Outcomes

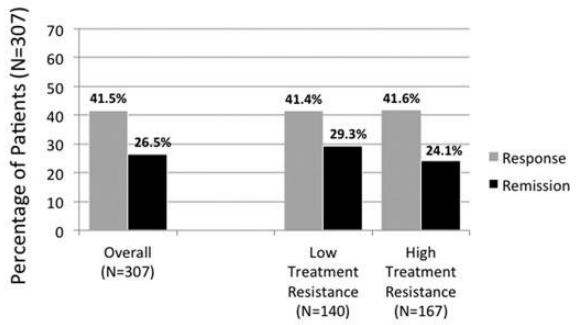


LOCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

Carpenter et al. 2012

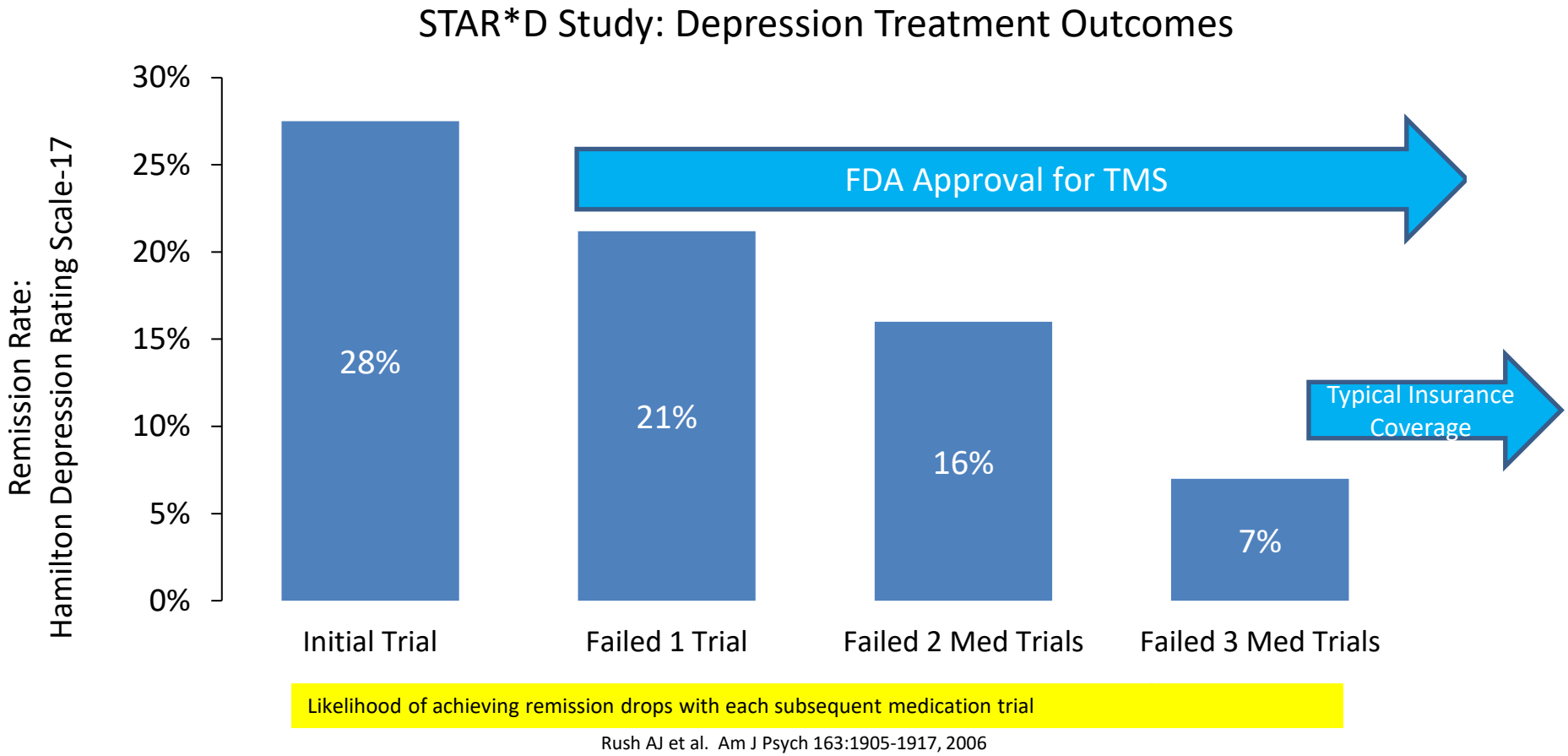
- 339 patient with MDD naïve to TMS
- Concurrent medications/therapy
- Response Rate: 41.5-58%
- Remission Rate: 26.5-37.1%
- Age and severity predict outcome
- Treatment-resistant not a predictor

IDS-SR Outcomes



LOCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

Why Consider TMS treatment for Depression?



Rush AJ et al. Am J Psych 163:1905-1917, 2006

Pivotal Study: TMS is FDA cleared for OCD

- 99 Patients, YBOCS ≧ 20
- 11 sites (3 countries)
- Response Rate: 30%
- Drop out ca. 12% both groups
- 1 patient SI in active group
- No seizures
- Protocol:
  - **Symptom Provocation**
  - DMPFC/ACC
  - H7 coil
  - 20Hz (2s on 20s off)
  - 100% leg MT
  - 2000 pulses (18min)
  - 6 weeks

FIGURE 2. Change from baseline in mean YBOCS score through the study for the active and sham dTMS treatment groups[a]

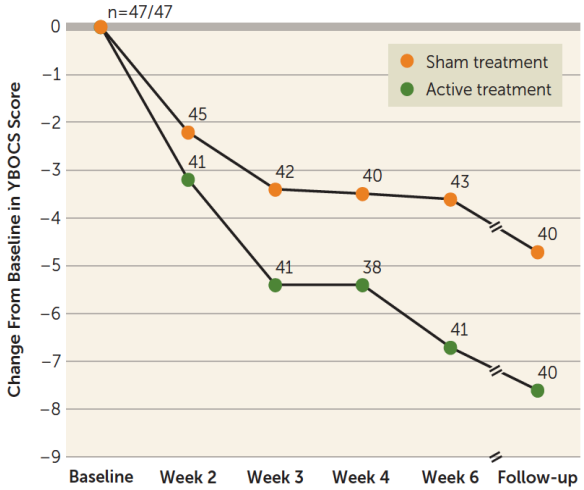
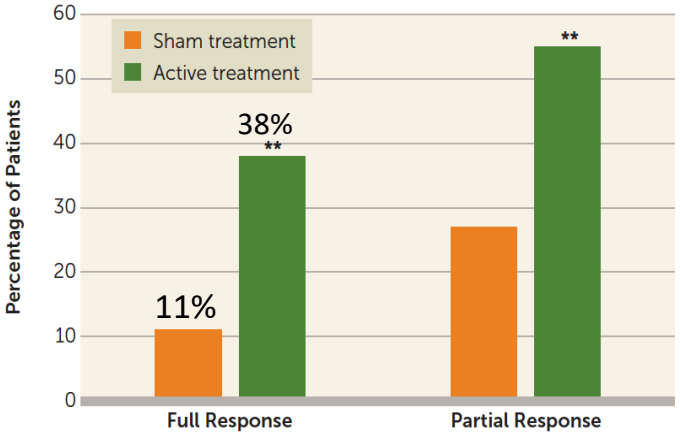


FIGURE 3. Rates of full response and individual distribution of responders and nonresponders according to YBOCS score at week 6 in the active and sham dTMS treatment groups[a]



Carmi et al. 2019

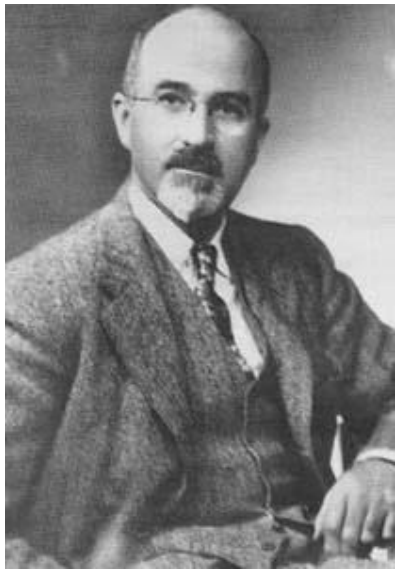
Summary

- TMS clinical applications: diagnostic and therapeutic
- TMS parameters
  1. Location
  2. Focality and Depth
  3. Frequency
  4. Pulse intensity
  5. Duration (session and course of treatment)
- Therapeutic rTMS (approved)
  - MDD: high-freq. Left DLPFC vs. low-freq. Right DLPFC
  - OCD -> high-freq. DMPFC (also low-freq. pre-SMA)
  - Migraines -> occipital pole single pulse TMS

Psychosurgery - 1930s

John Fulton

Egas Moniz

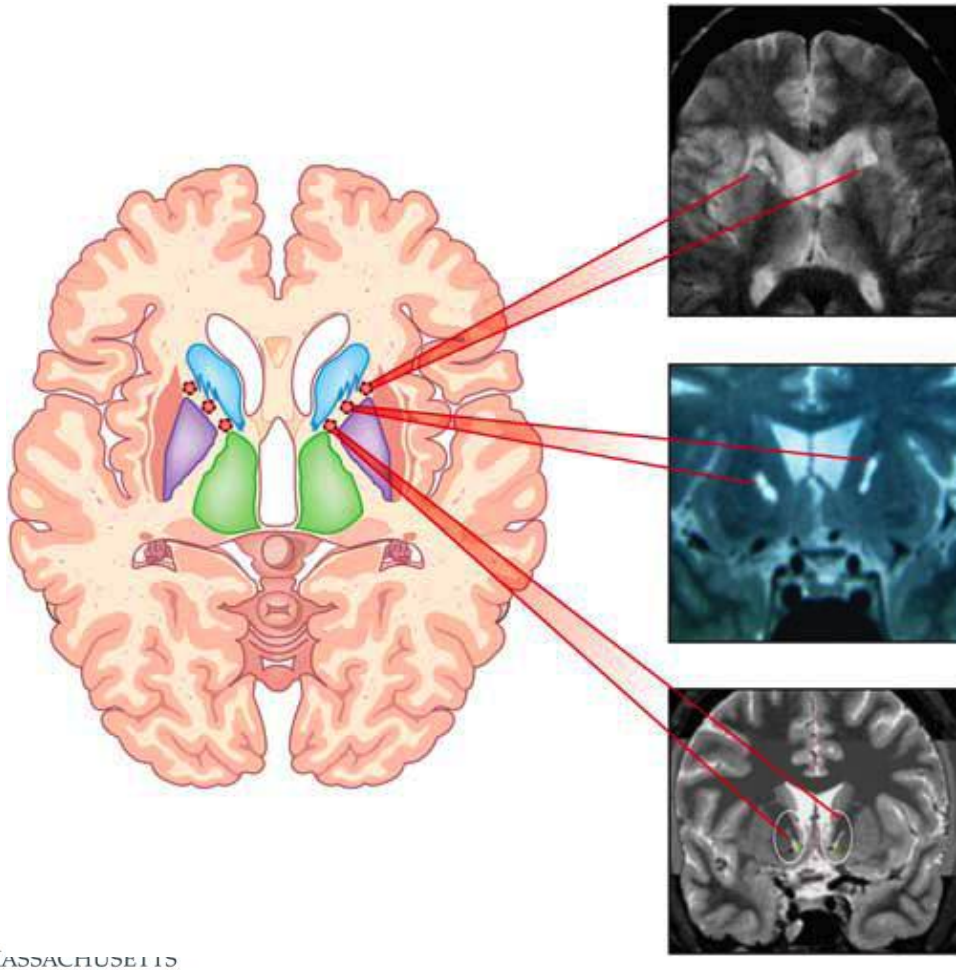


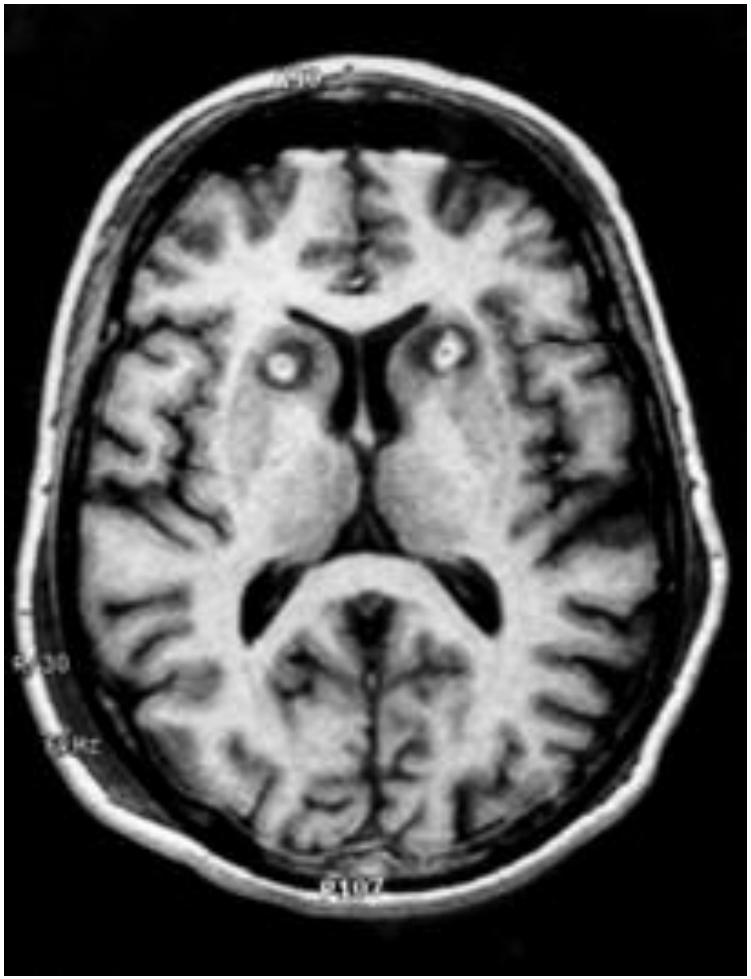
Walter Freeman

Leukotomies today

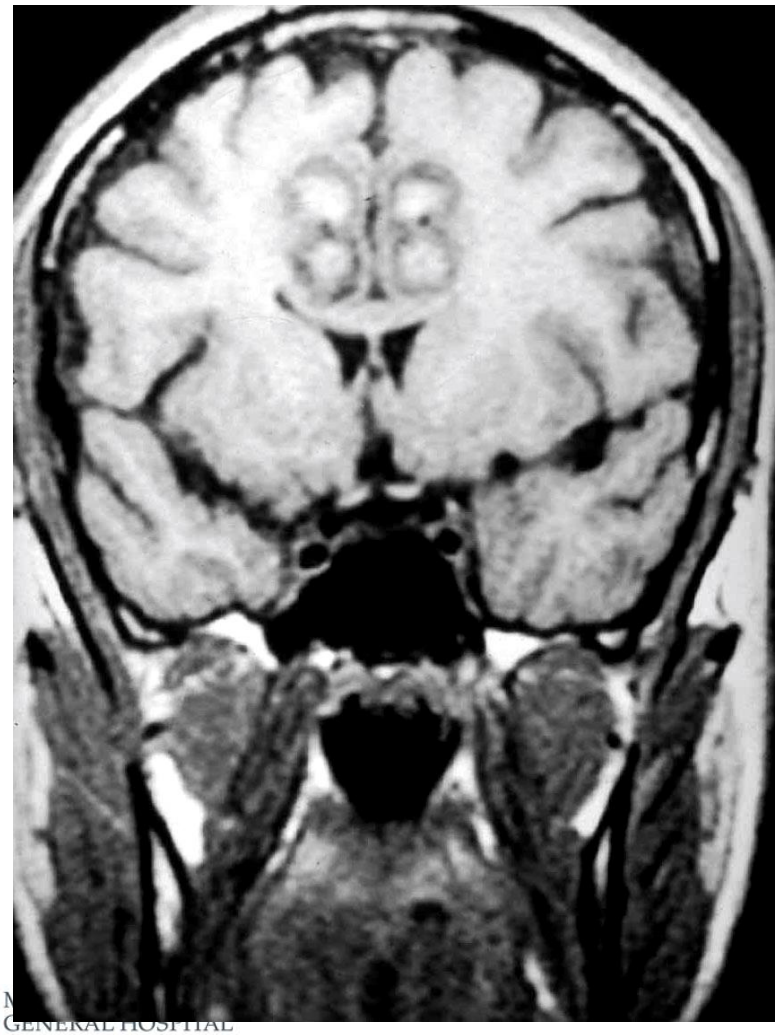
- Disorders: MDD, OCD
- Interventions
  - 1) Anterior Capsulotomy
  - 2) Anterior Cingulotomy
  - 3) Subcaudate Tractotomy
  - 4) Limbic Leukotomy (combination of 2 and 3)
- Methods
  - MRI-guided Thermocoagulation vs
  - Gamma knife (ambulatory)

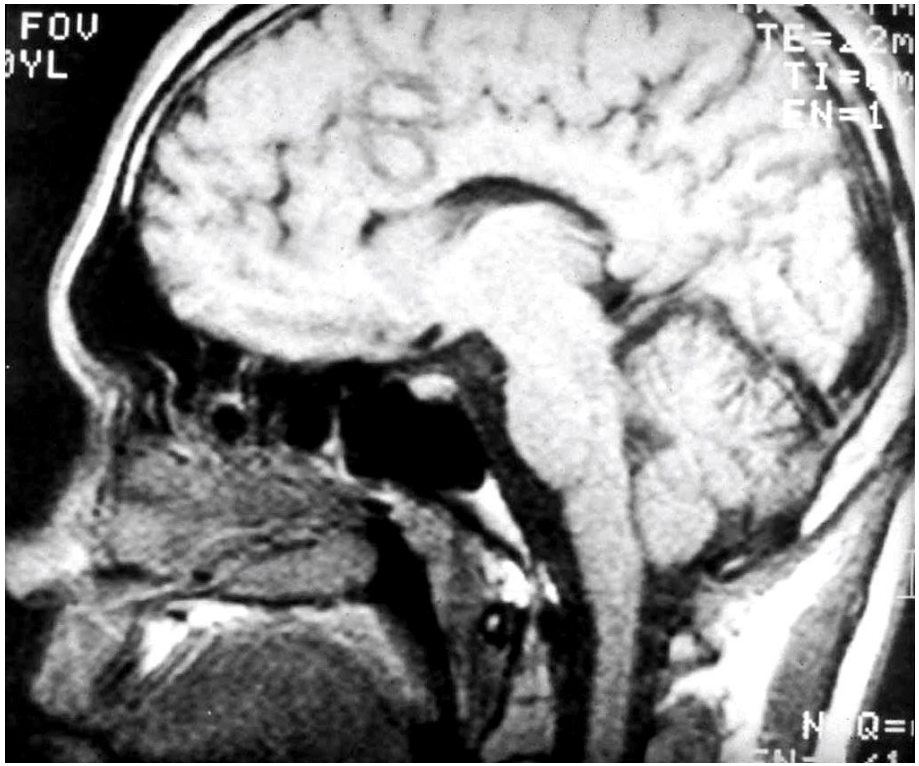
Anterior Capsulotomy



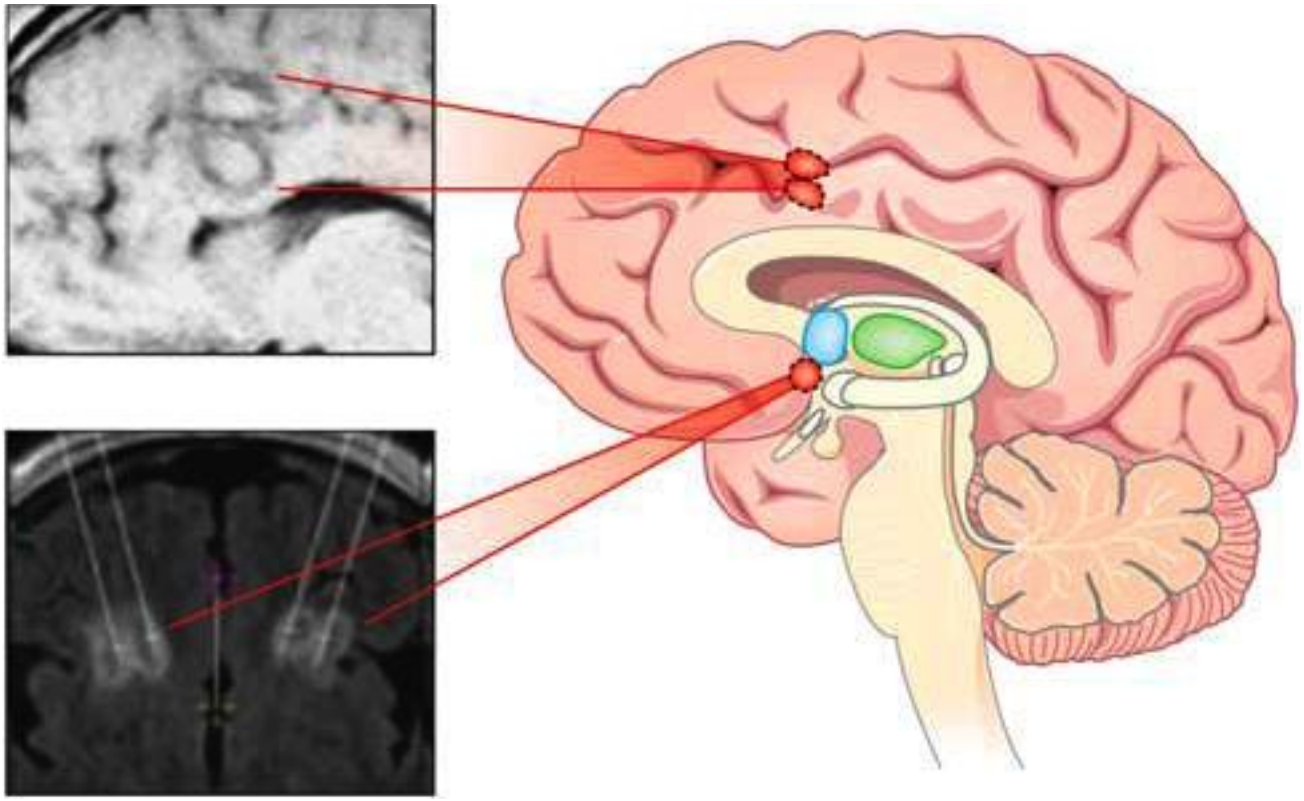


Anterior Cingulotomy





Limbic Leukotomy

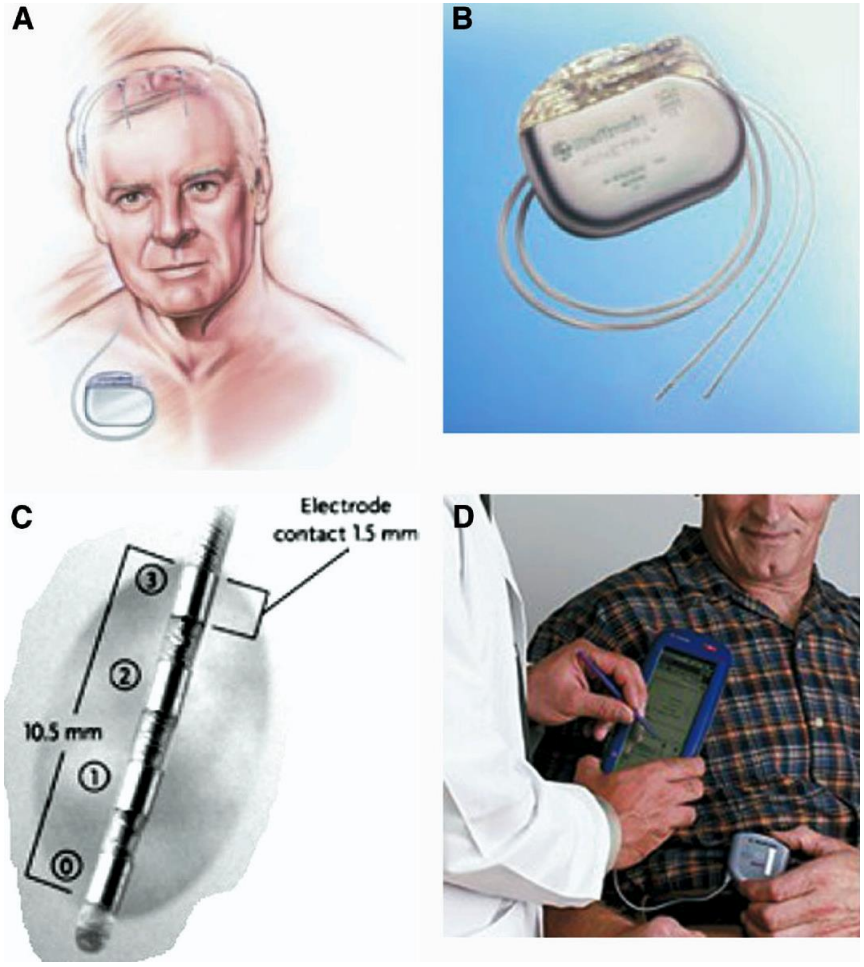


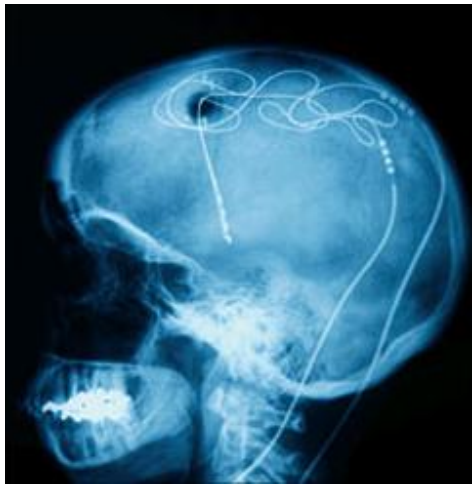
Cingulotomy

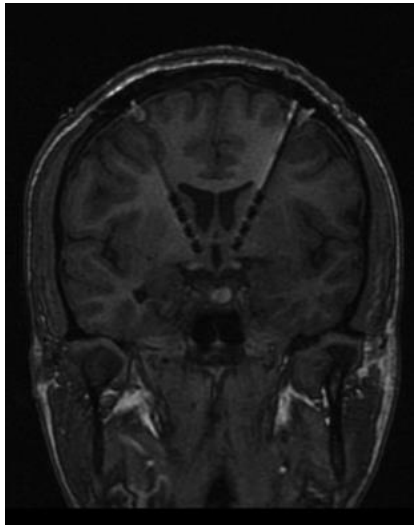
+

Subcaudate Tractotomy

DBS technology







DBS vs. Leukotomy

- Advantages
  - Adjustability (Frequency, Voltage, Pulse Width, Electrode Position)
  - Nondestructive/Reversible
  - Capacity for Blinding
- Demonstrated better safety for PD, not yet in Psychiatry
- But… need for frequent f/u visit, battery replacement (risk relapse, repeated minor surgeries), cost. Leukotomy still an option!!

DBS Parameters

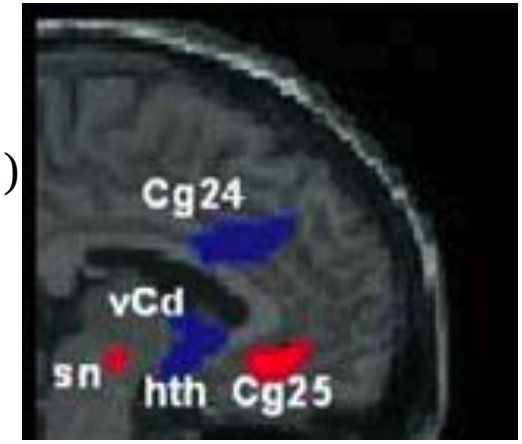
- Location
- Amplitude
- Frequency
- Pulse Width
- Shape of electric field

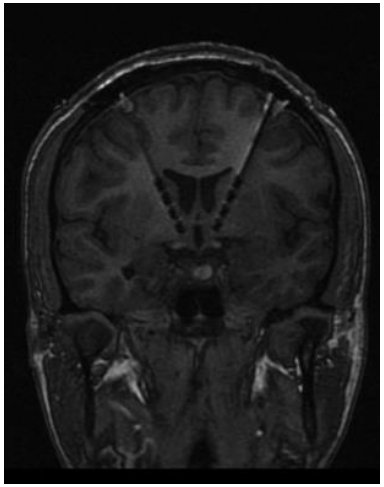
DBS Target Population

- Severe Treatment-Resistant OCD (MDD experimental)
  - Failed at least 4 adequate trials of medication, including different classes and augmentation strategies
  - Failed adequate trial of evidence-based psychotherapy
  - Failed ECT (for MDD)
- Approval by Multidisciplinary Committee

4 main DBS targets for TR-MDD

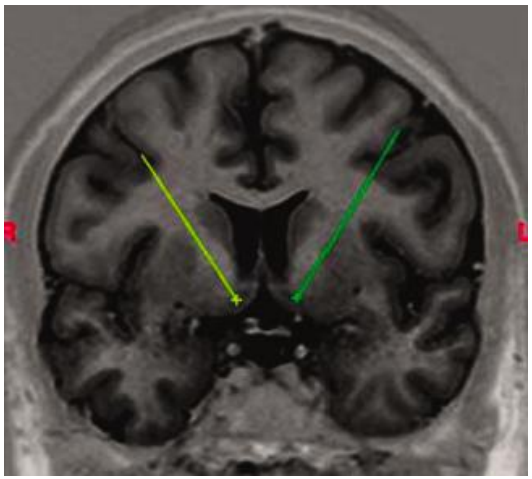
Subgenual Cingulum Cg25 (Mayberg et al.)
55% response rate

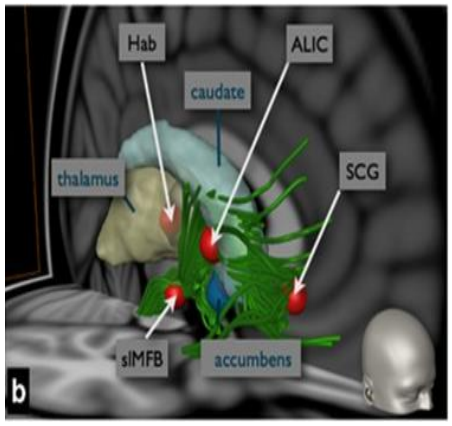




Ventral Striatum / Ventral Capsule (Malone, Dougherty et al)
53% response rate

Nucleus Accumbens (Schlapfer et al)
33% response rate

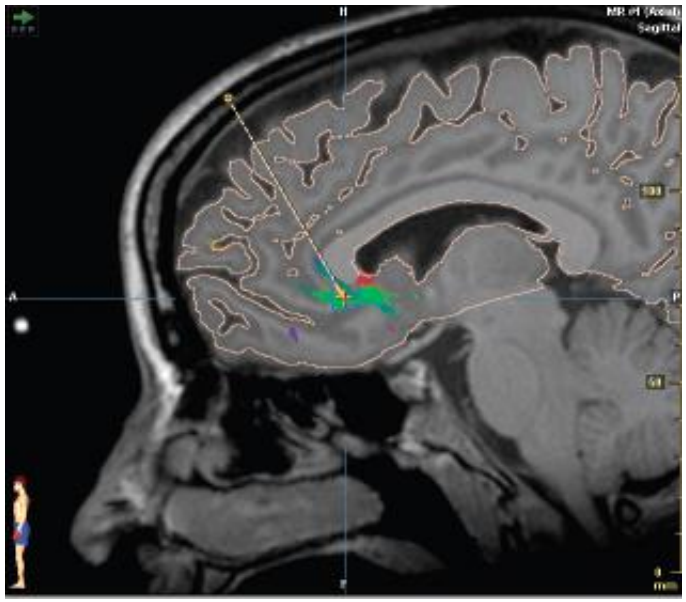




Middle Forebrain Bundle (Coenen et al) 100% response

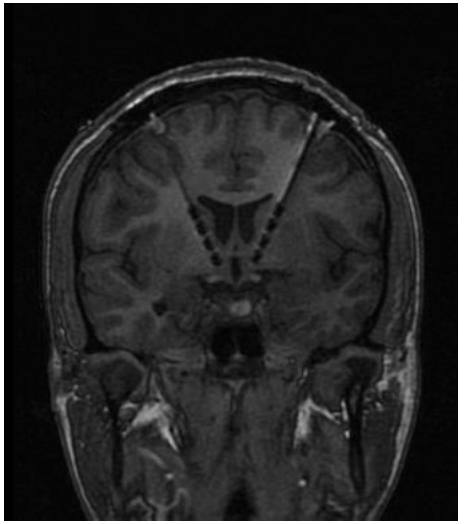
Subgenual Cingulate (CG25)

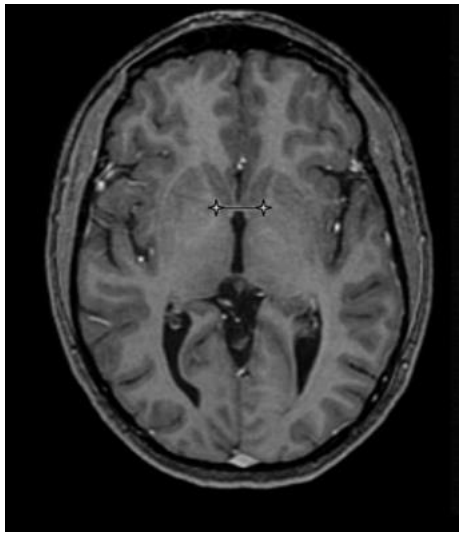
- First open label study in 2005 (6 pts) and a follow up in 2008 (20 pts)
- Approximately 55% response rate at 6mo and 12mo
- Core mood symptoms respond faster
- Neurovegetative symptoms take longer
- However… pivotal industry-sponsored RTC halted following interim futility analysis



Anterior Capsule / Ventral Striatum

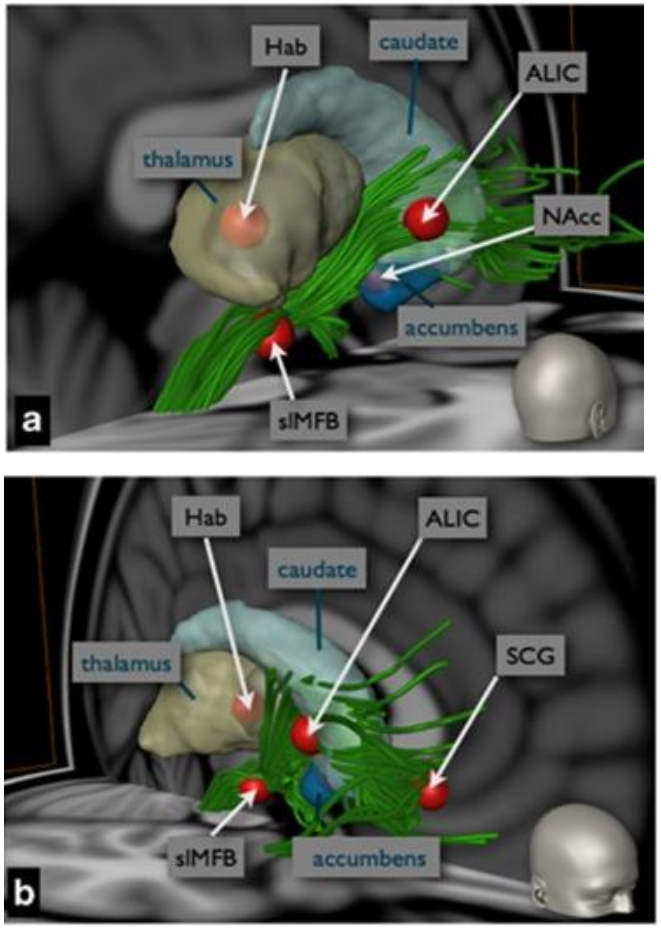
- Common DBS site for earlier studies in OCD
- Documented changes not only in OCD but also Mood symptoms
- Multicenter (MGH, Brown, Cleveland) open-label trial in 2009 (15 pts)
- Most Ventral contacts tend to show better response
- However… pivotal industry-sponsored RTC was negative.





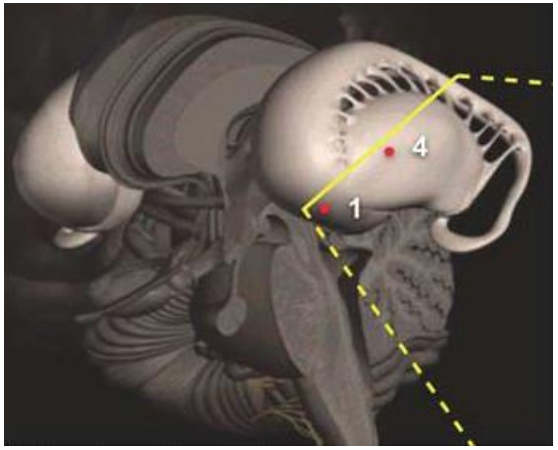
Medial Forebrain Bundle (MFB)

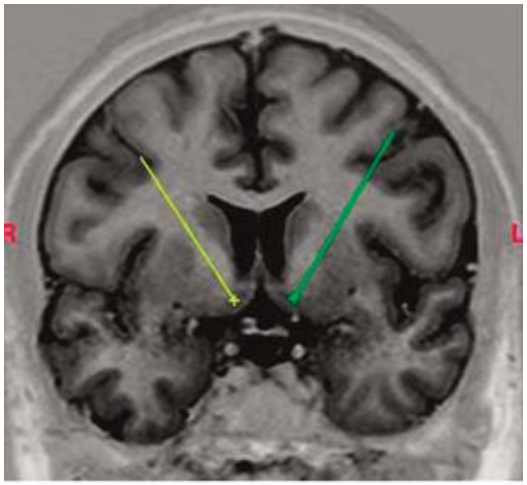
- Six of seven TRD patients met criteria for response after only 7 days of stimulation
- Initial proof of concept
- Recent small RTC (n=16) reported 100% response rate (50% remitters)



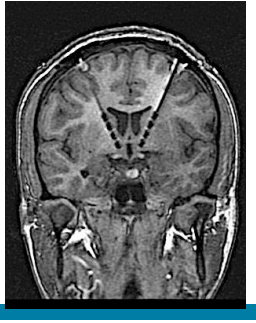
Nucleus Accumbens

- Location very similar to AC/VS (Nac = Ventral Striatum)
- Schlaepfer et al. (Bonn, Germany) published first open-label study in 2008 (3pts, 33% response)
- Report significant reduction in Anhedonia, which responds earlier than other symptoms of MDD



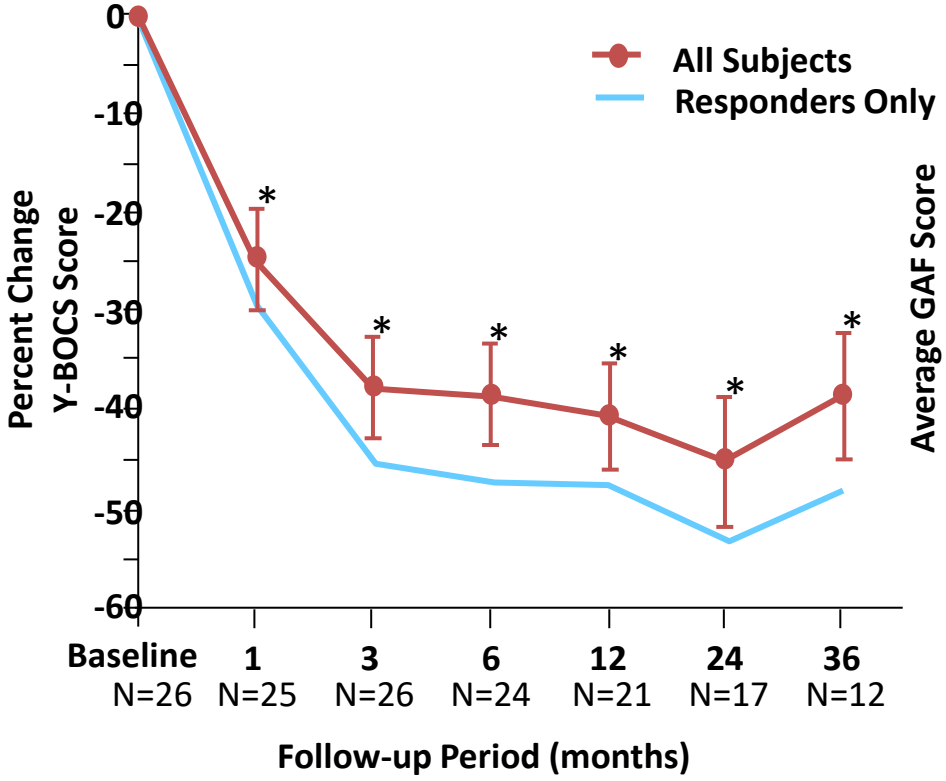


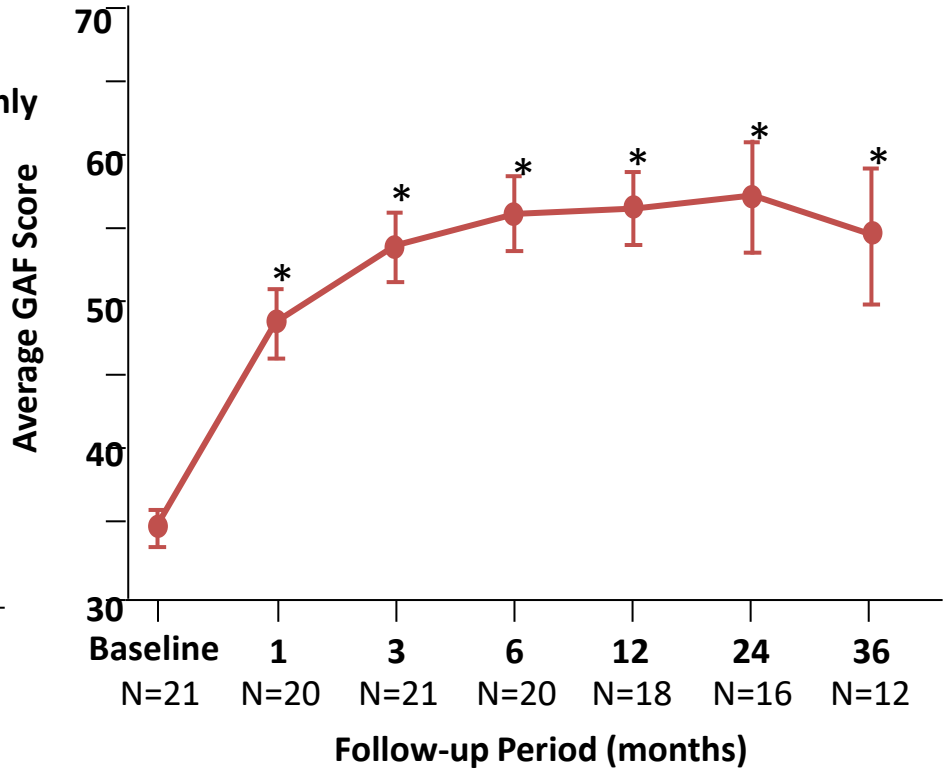
DBS (VC/VS) for OCD



Approved by FDA in 2009 (HDE mechanism)

Reimbursed by third party payers

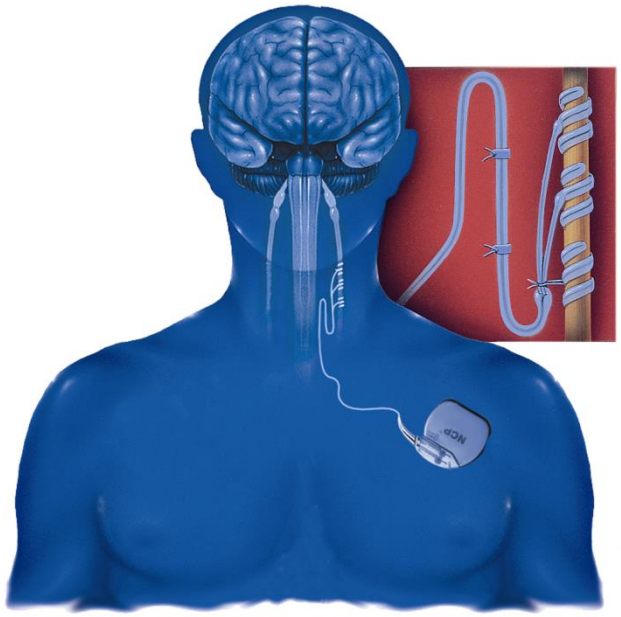


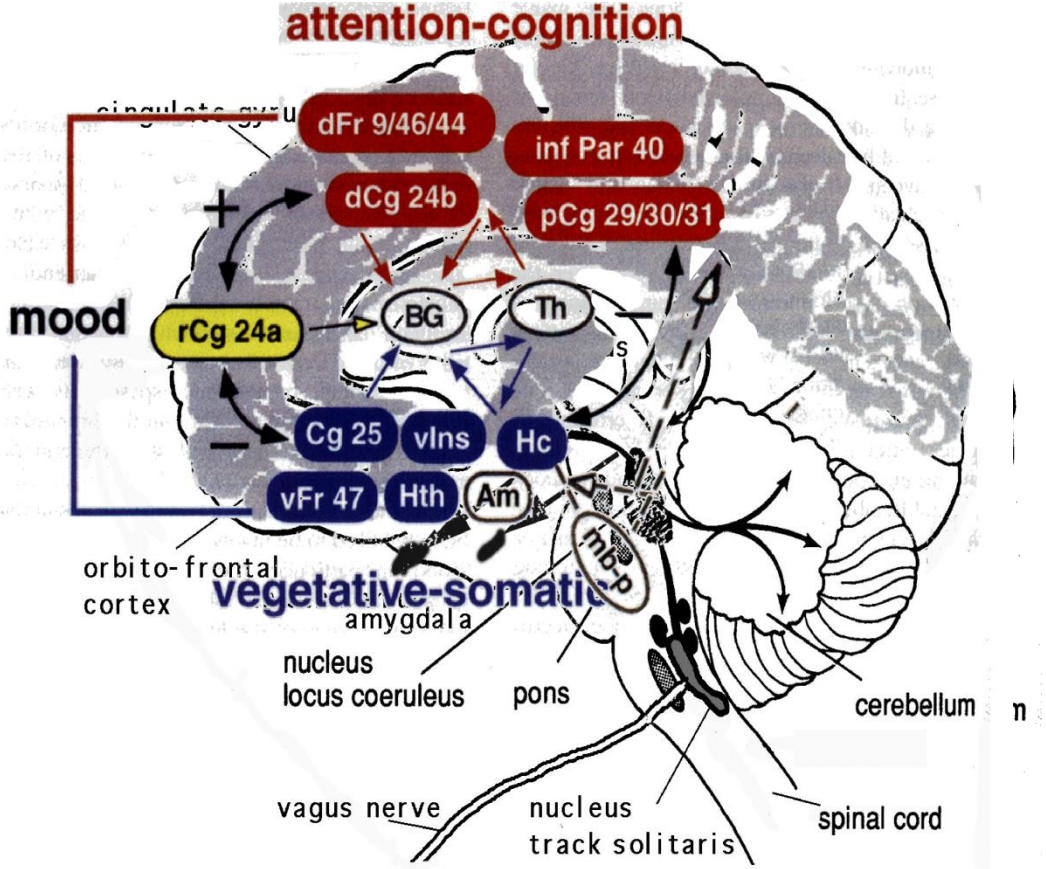


* Within-subject change statistically significant ($p \leq .001$, two-sided test).

VNS Therapy for Treatment-Resistant Depression

Vagus Sensory Afferents Go to Midbrain, Limbic, and Prefrontal Structures

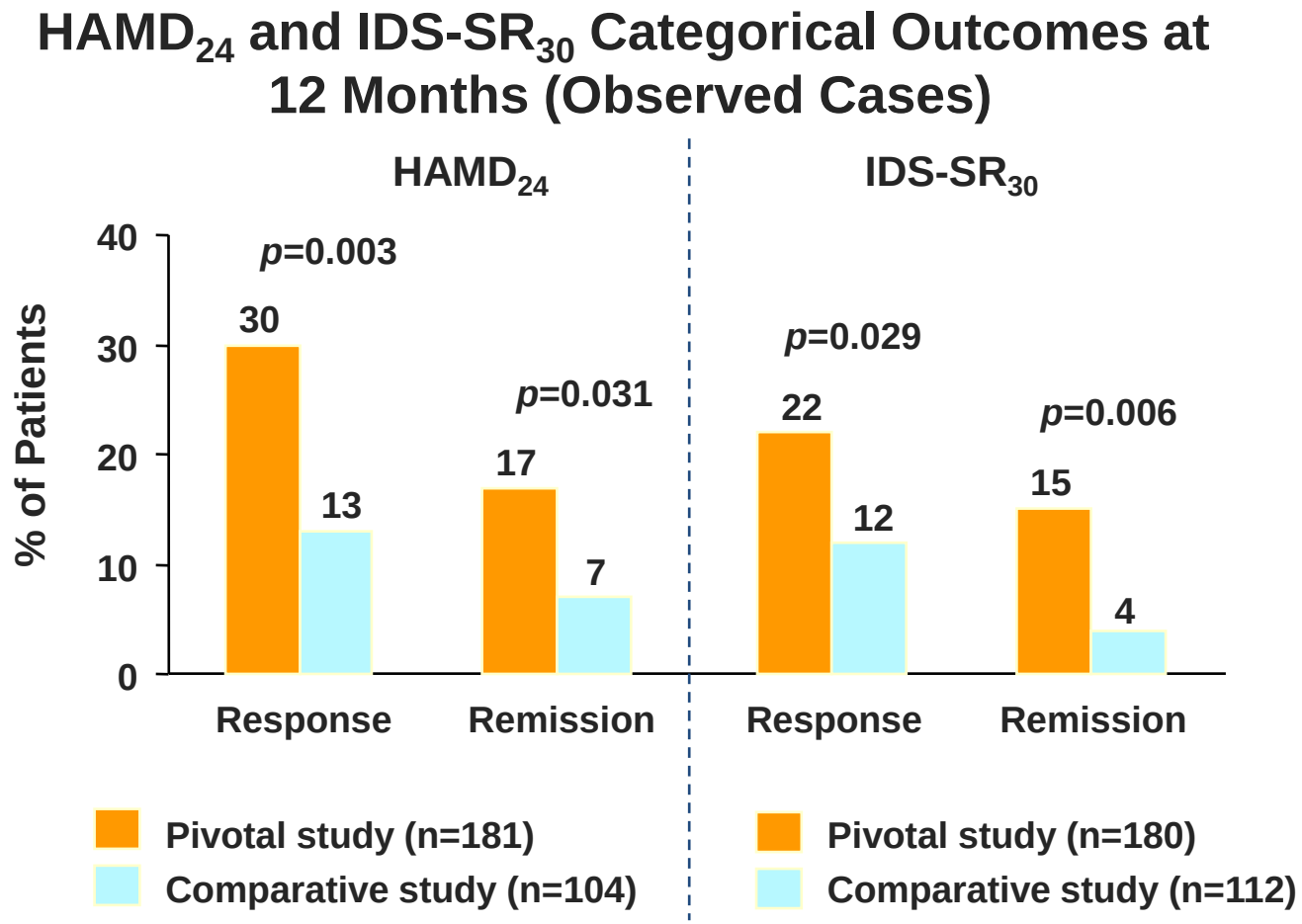




VNS for TRD

- 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 is currently virtually nonexistent

Pivotal Study vs Comparative Study: Secondary Analysis

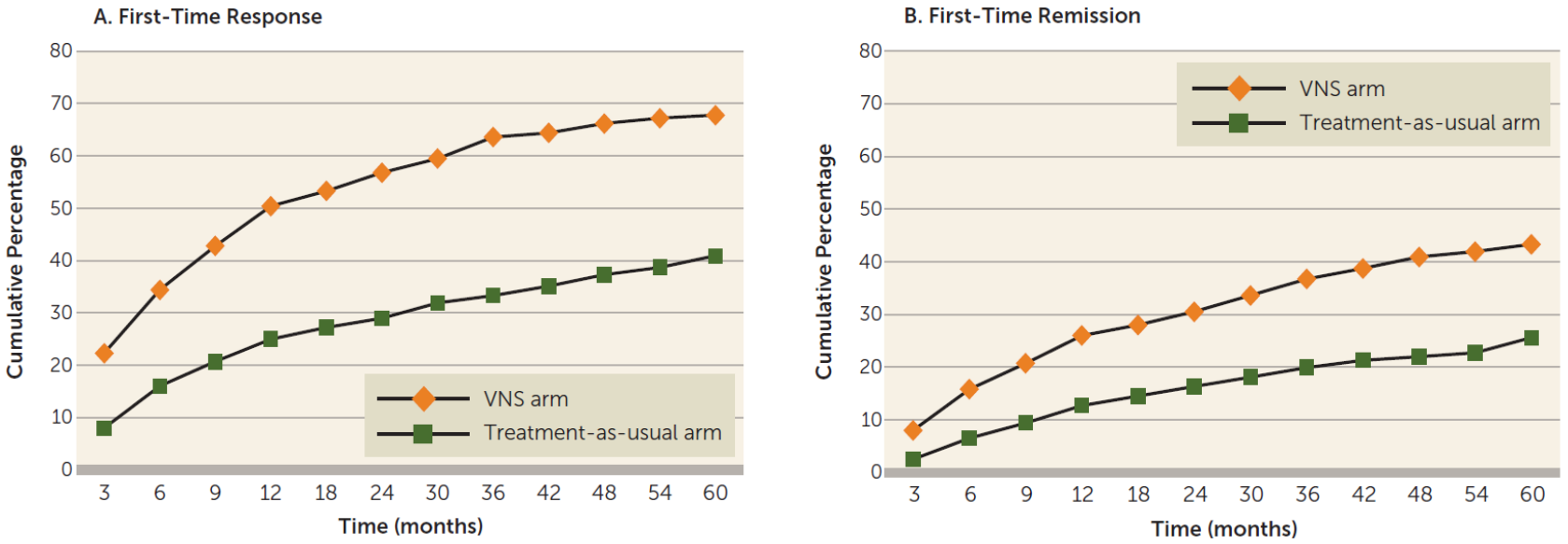


FDA Approved 2005

George MS, et al. *Biol Psychiatry*. 2005;58:364-373.

Newer VNS for TRD Data

- VNS Registry study included 795 pts with TRD treated with TAU alone or TAU + VNS and followed for 5 years



CMS Reconsideration resulted in initiation of controlled clinical trial in 2019

Conclusions

- Circuit-based paradigm to understand the pathophysiology of Affective Disorders brings not only new knowledge but also therapeutic clinical applications
- Several device-based interventional strategies are FDA approved: some non-invasive (e.g. TMS) and some invasive (e.g. VNS, DBS)
- They all target circuits selectively to induce plasticity and change physiology
- Beyond therapeutic tools, these interventions are also useful for the understanding of mechanisms of disease and the development of clinical tools such as biomarkers
- As we advance our understanding of the pathophysiology of other Neuropsychiatric disorders, the applications of these interventions will expand

Thanks!