Role of Neurostimulation in Depression

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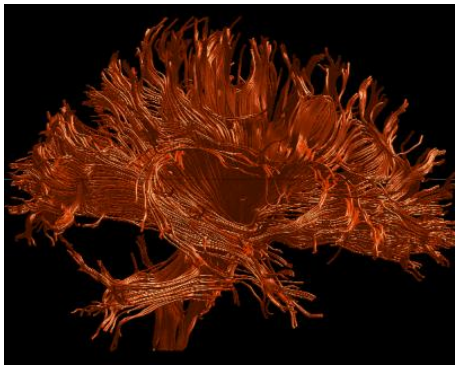
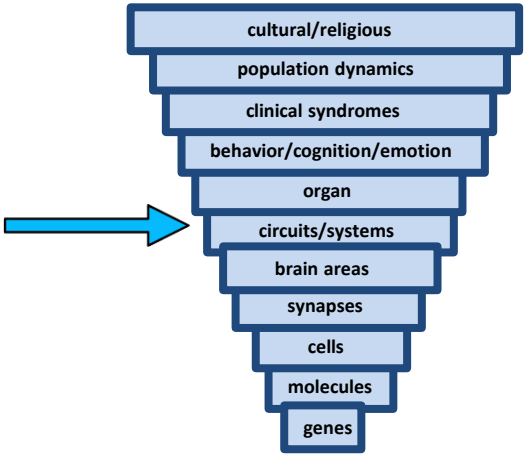
Outline

- A Clinical Neuroscience Paradigm: Circuits and Clinical Dimensions
- General Principles of Neuromodulation: Pacemakers in the Brain
- TMS Parameters and Mechanisms
- Introduction to Applications: Diagnostic and Therapeutic

Neuropsychiatry: Disorders of Connectivity

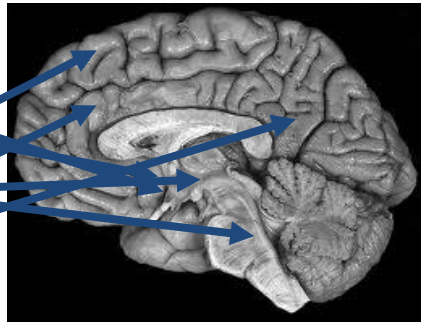




Neuroanatomy of MDD

From Clinical Dimensions to Brain Circuits

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



Clinical/Behavioral dimensions shared by different syndromes!

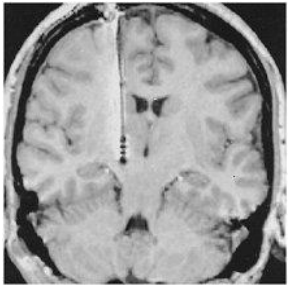
Brain Stimulation – Neuromodulation

Invasive

Deep Brain Stimulation (DBS)

Vagal Nerve Stimulation (VNS)

Epidural Stimulation (ES)



Convulsive

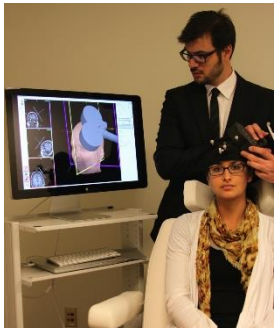
Electroconvulsive Therapy (ECT)

Magnetic Seizure Therapy (MST)

Noninvasive

Transcranial Magnetic Stimulation (TMS)

Transcranial Direct Current Stimulation (tDCS)

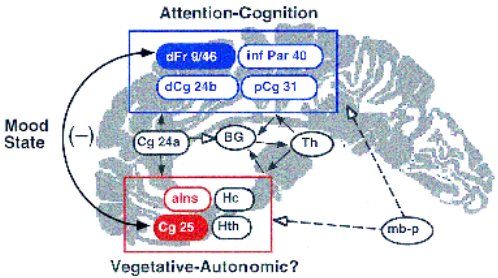


Therapeutic Neuromodulation and the FDA

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
Transcranial Current Stimulation	MDD, TBI, Stroke Rehabilitation, etc.	Experimental

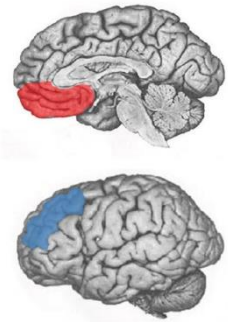
Neuromodulation: Need to know…

The circuit(s)



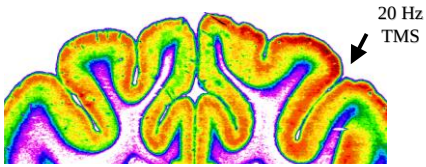
Mayberg et al., 2010

The target(s)



Koenigs et al. 2009

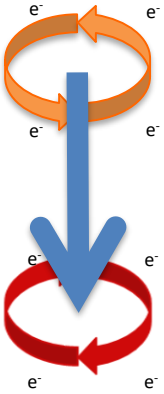
Direction of modulation



Valero Cabre et al., 2008

Transcranial Magnetic Stimulation

1831 Faraday's Electromagnetic Induction

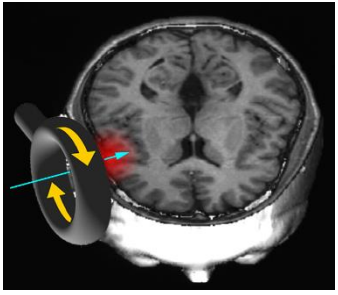


Primary Electric Current

Magnetic Field

Secondary Electric Current

Anthony Barker 1984



Transcranial Magnetic Stimulation

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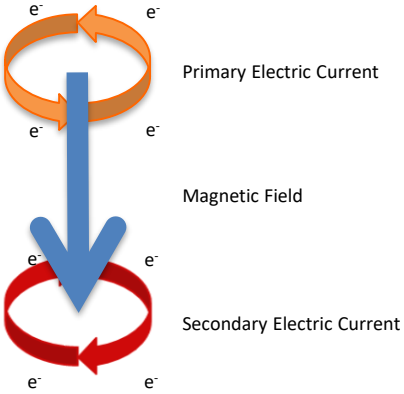
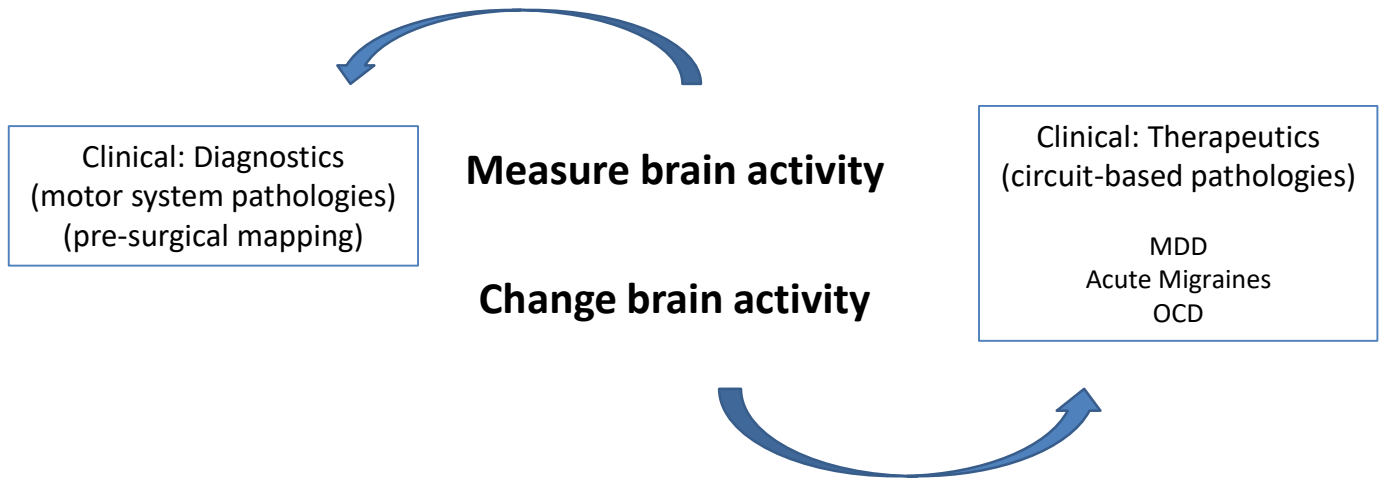


TMS Applications

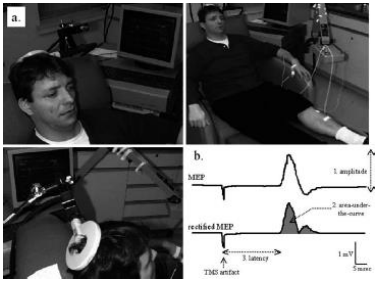


Relevant TMS Parameters

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)

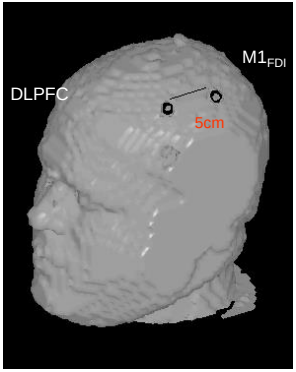
Localization: Non-Imaging Based

Motor & Phosphene Threshold

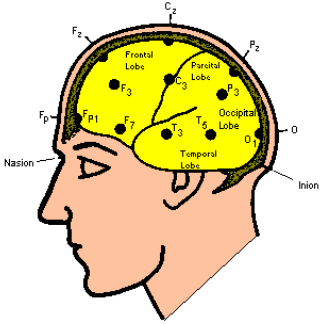


Tormos et al., 2008

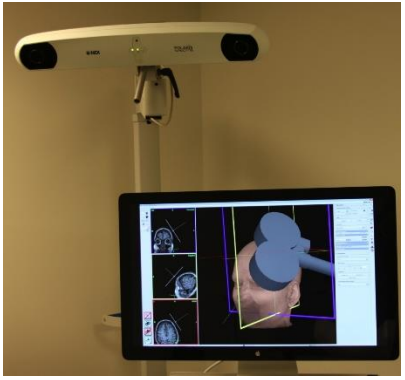
DLPFC Localization



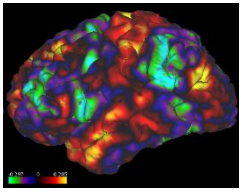
10-20 EEG coordinate system



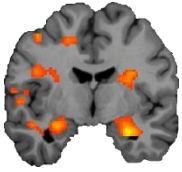
Localization: Neuronavigation



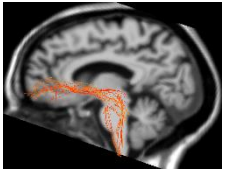
fcMRI

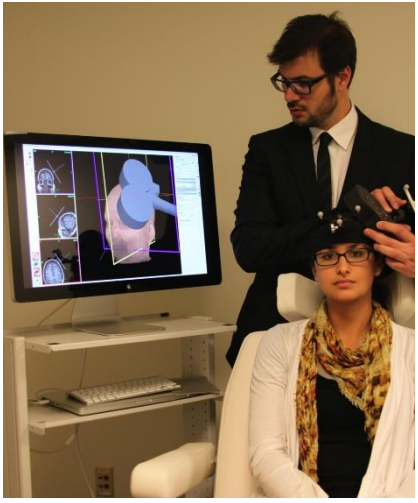


Task fMRI



DTI

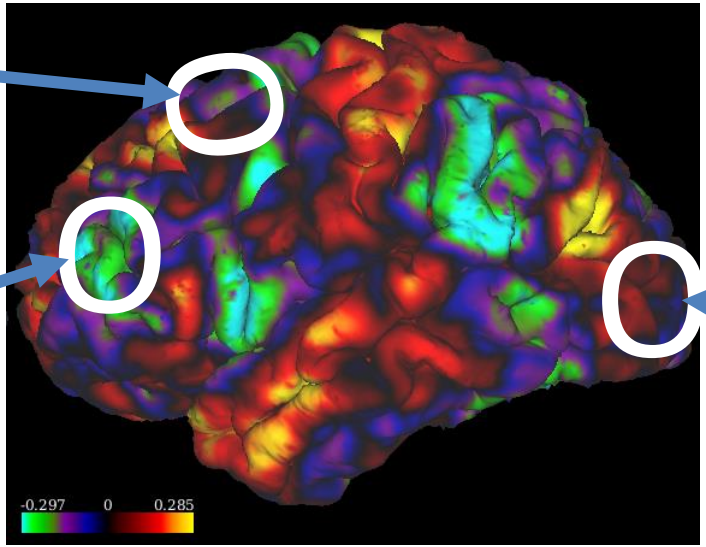




Therapeutic Targets

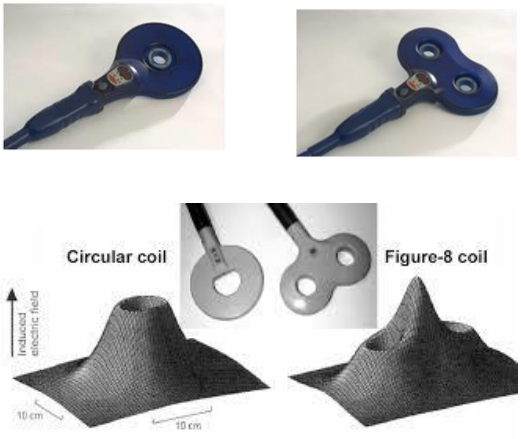
OCD Target:
DMPFC/pre-SMA

MDD Target:
DLPFC



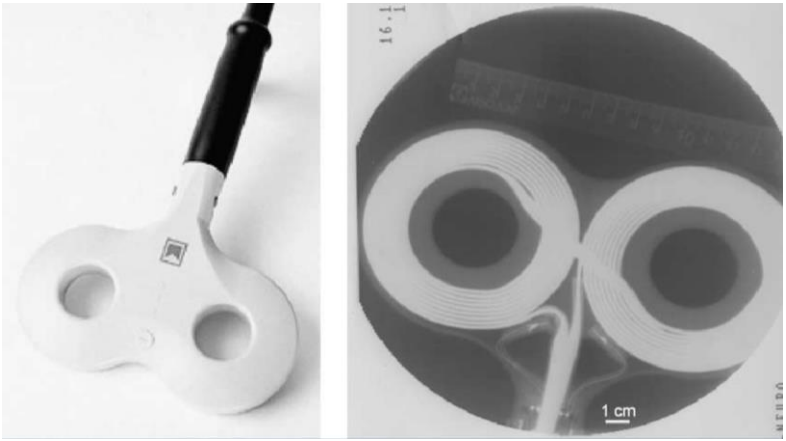
Migraine Target:
Occipital pole

Focality: TMS Coils



Tormos et al., 2008

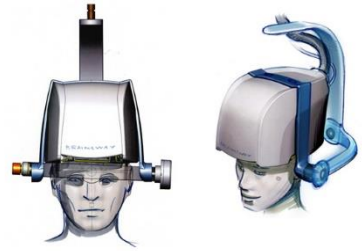
TMS Coil Architecture



Tielscher & Kammer 2004

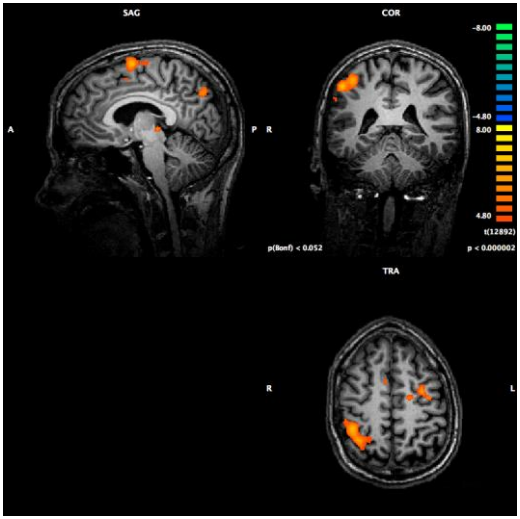
Depth of Stimulation

Direct Deep Modulation: H-Coil



Chosen design concept

Trans-synaptic deep modulation: network effects



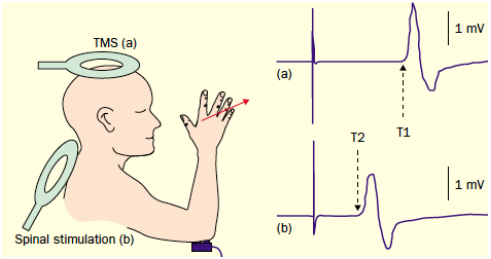
Basic Types of Stimulation

- Single Pulse: Disrupts activity with high temporal and spatial resolution (diagnostic applications: e.g. pre-surgical mapping)

- Paired Pulse: Elicits neuroplastic mechanisms of inhibition or faciliation (diagnostic applications: e.g. clinical neurophysiology)

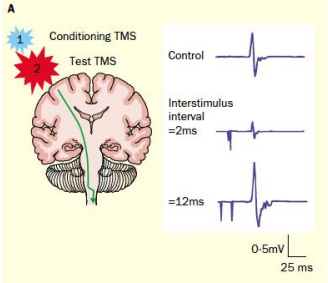
- Repetitive Stimulation (rTMS): Modulates (decreases or increases) neural activity of areas and networks with lasting effects
  - Low frequency ~1Hz --> decrease activity (LTD-like)
  - High frequency 5-20Hz --> increase activity (LTP-like)
  - New Protocols: intermittent and continuous Theta Burst Stimulation (TBS)

Single & Paired-Pulse TMS



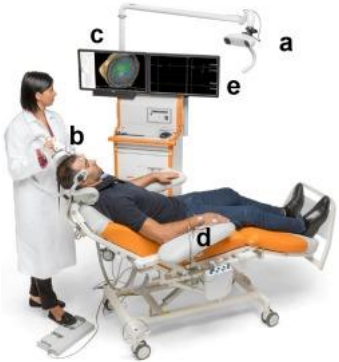
- Motor Threshold
- Input/Output Curves
- Central Conduction Time
- Silent Period

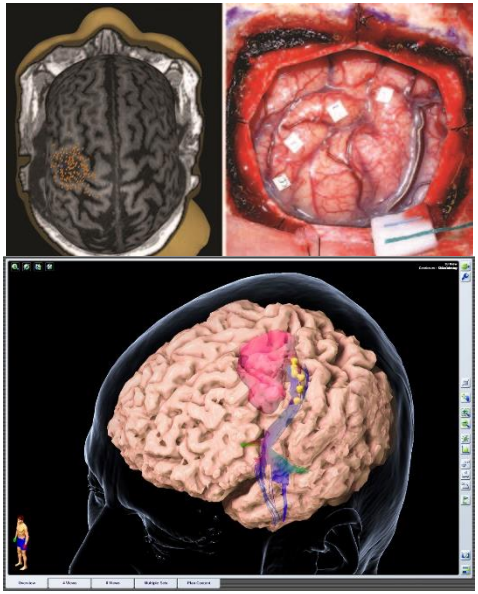
Kobayashi 2003



- SICI: Short Interval Cortical Inhibition
- ICF: Intracortical Facilitation

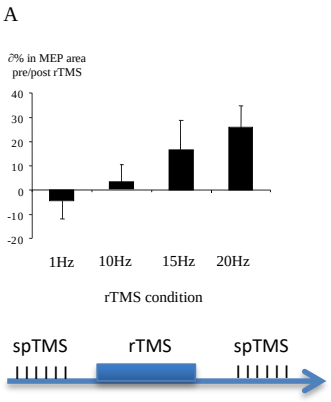
Diagnostic: Pre-Surgical Mapping

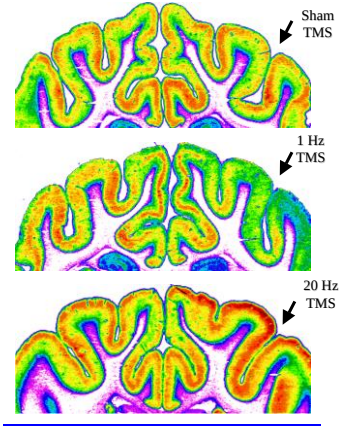




Repetitive TMS: Neuromodulation

Frequency-Dependent Effects





(A) Change in MEP in healthy humans after rTMS (Maeda et al.)
(B) Metabolic changes (2-deoxyglucose uptake) in the cortex of the cat after rTMS (Valero-Cabré et al.)

Repetitive TMS: Neuromodulation

- **Neural Pacemaker:** Forces a population of neurons to fire at a specific frequency, changing excitability and functional connectivity both locally and within a given network

- Chronic vs. Discrete Stimulation
- Invasive vs Noninvasive
- All aim to induce adaptive neuroplasticity

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

Safety: Seizures

Principal Adverse Effect: Risk of Seizure

- Always during session, never after TMS.
- Does not develop into Epilepsy
- Safety Guidelines established and published
- 20 reported cased out of 300.000 sessions
- 7 cases in MDD patients treated with Neuronetics® system since 2008 FDA approval (out of 250.000< sessions in 8000< patients) (report 2013)
- Risk is 1 in 30.000 sessions or 1 in 1000 patients

Safety: Others

- Metallic implants
- Headache
- Local discomfort
- Facial muscle twitching
- Auditory impairment
- Drugs/diseases changing cortical excitability?

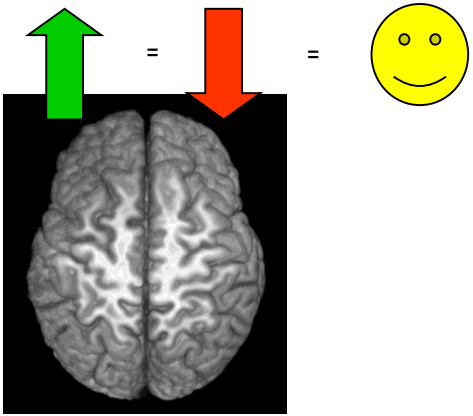
Therapeutic Applications: MDD

- Early PET data argued for an overall hypofrontality in Depression, with additional hemispheric unbalance
- rTMS to DLPFC has been shown to affect mood (in healthy and diseased individuals)

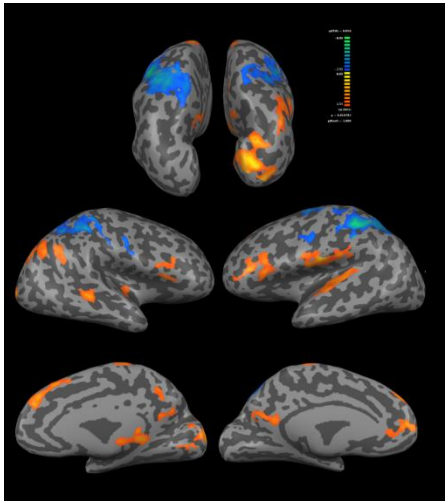
Depression Rx Strategy:

-Left: High Frequency (5-20 Hz)

-Right: Low Frequency (1 Hz)



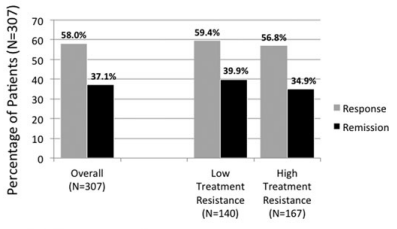
rTMS Modulates Brain Circuits



Camprodon et al. 2010

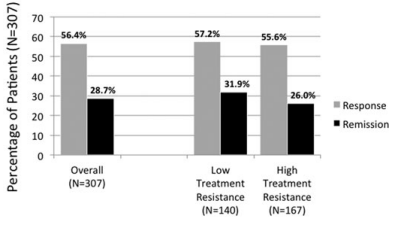
Effectiveness Naturalistic Studies

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

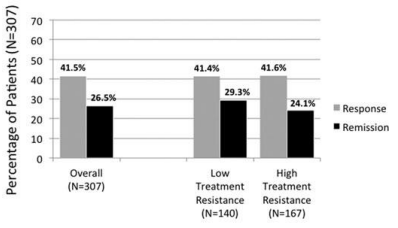


LOCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

Carpenter et al. 2012

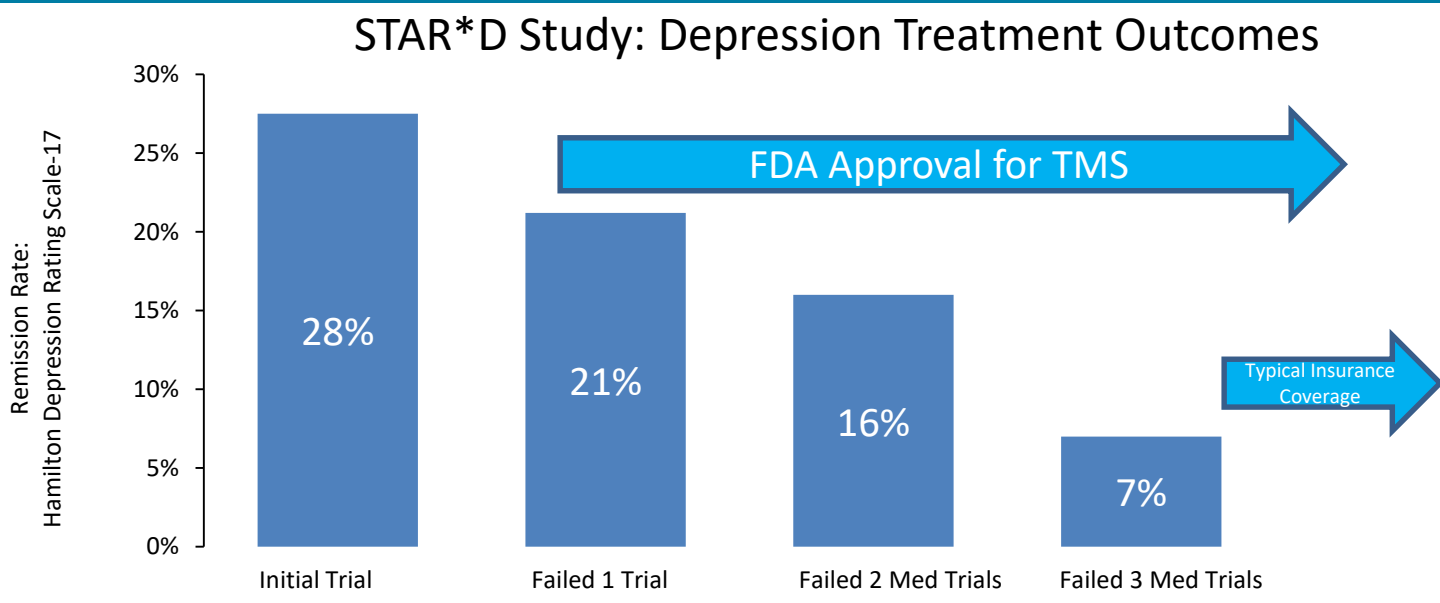
- 339 patient with MDD naïve to TMS
- Concurrent medications/therapy
- Response Rate: 41.5-58%
- Remission Rate: 26.5-37.1%
- Age and severity predict outcome
- Treatment-resistant not a predictor

IDS-SR Outcomes



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

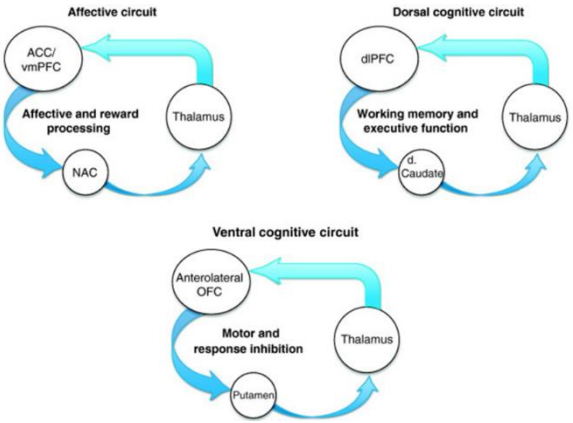
Why Consider TMS Treatment for Depression?



Likelihood of achieving remission drops with each subsequent medication trial

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

Beyond Depression



Milad & Rauch 2010

Approved indications

- MDD
- OCD
- Acute Migraines
- Smoking Cessation

Experimental Indications

- Any Circuit-based brain conditions

Summary

- Clinical neuroscience paradigm: formulate a clinical problem based on dimensions and circuits.
  - Plasticity as a pathophysiological mechanism and also therapeutic mechanism of action
- Neuromodulation: Invasive, Convulsive and Non-Invasive
- TMS clinical applications: diagnostic and therapeutic
- TMS parameters (and safety):
  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

Thanks!