TMS and Imaging

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- Consultant: Mifu Technologies, Neuroelectrics, LivaNova

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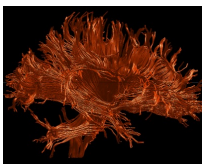
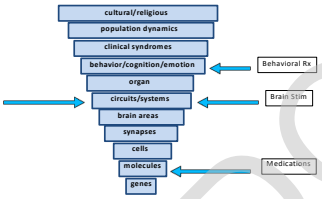
Neuropsychiatry: Disorders of Connectivity





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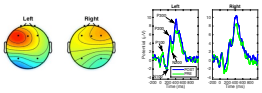
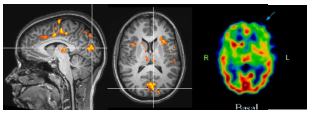
Functional Neuroimaging Methods

Electrophysiologic: EEG/MEG



Metabolic and/or Vascular

- **PET/SPECT**
- **fMRI**
- **NIRS**



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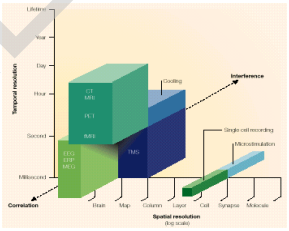
2 Axis of Resolution… or 3?



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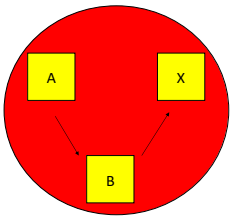
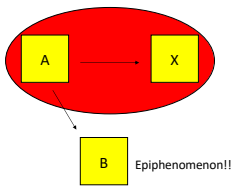
3rd Axis: Causality





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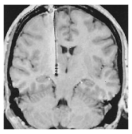
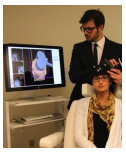
Brain Stimulation - Neuromodulation

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)



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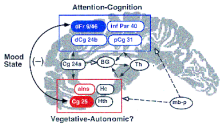
Neuromodulation: Need to know…

The circuit(s)

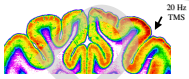


Mayberg et al., 2010

The target(s)

Koenigs et al. 2009

Direction of modulation



Valero Cabre et al., 2008

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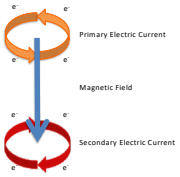
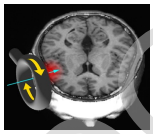
Transcranial Magnetic Stimulation

1831 Faraday's Electromagnetic Induction

Anthony Barker 1984





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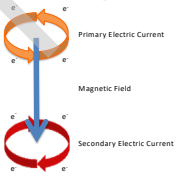

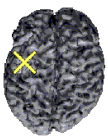

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TMS Applications

Clinical: Diagnostics
(motor system disorders)
(pre-surgical mapping)

Measure brain activity

Change brain activity

Clinical: Therapeutics
(circuit-based pathologies)

MDD
Acute Migraines
OCD
Smoking Cessation

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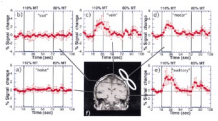
TMS limitations

- Where to stimulate?

- What does TMS do to the Brain? Only behavioral measures? Beyond the black box approach.



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Functional Neuroimaging vs. TMS

Neuroimaging	TMS
Correlational (cannot establish causality)	Interventional (and thus causal)
Measures whole-brain activity	Measures behavioral outcomes

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Why Combine TMS and Neuroimaging?

- Plan, guide and document localization of TMS → Neuroimaging BEFORE TMS
- Develop circuit predictor biomarkers → Neuroimaging BEFORE TMS
- Measure neurobiological effects of TMS, beyond cognitive and behavioral outcomes → Neuroimaging DURING TMS / Neuroimaging AFTER TMS

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TMS-fMRI vs PET/EEG

- Vs. TMS-PET
  - MRI: better spatio-temporal resolution
  - MRI: no need of radioligands (better potential for repeated measures)
  - PET: neurotansmiter dynamic or more complex biological process
- Vs. TMS-EEG
  - MRI: better spatial resolution
  - EEG: better temporal resolution
  - MRI: ability to measure subcortical structures with greater detail (anatomy)
  - EEG: diversity of physiological measures in frequency and time domain

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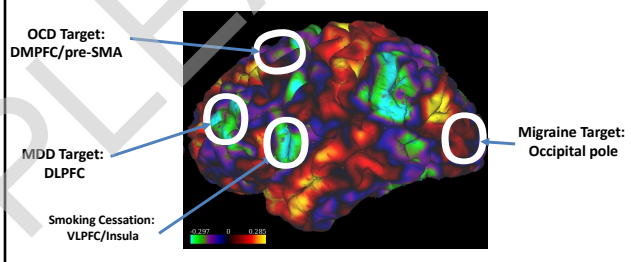
Anatomy: Therapeutic Targets



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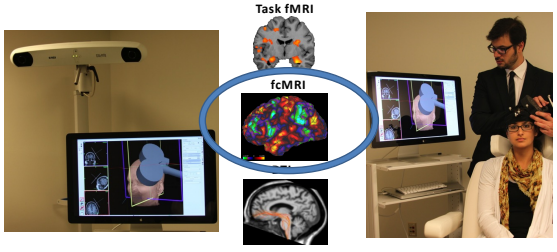
Localization: Stereotactic Neuronavigation



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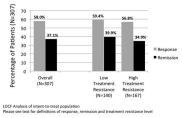
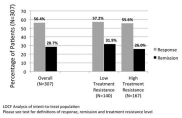
MDD Effectiveness: Naturalistic Studies

CGI-S Outcomes



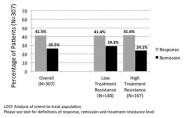
PHQ-9 Outcomes



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%

IDS-SR Outcomes



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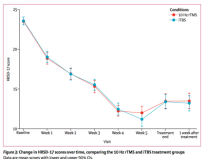
Group Level fcMRI Target: Prospective Trial

Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial



Response Rate: 39%-49%
Remission Rate: 20%-32%

No different than 5cm rule

FDA cleared in 2013

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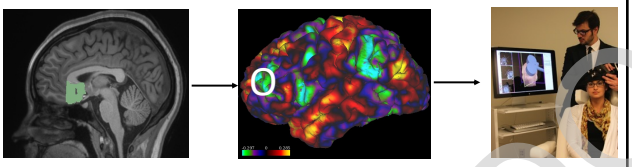
Individualized fcMRI-guided TMS



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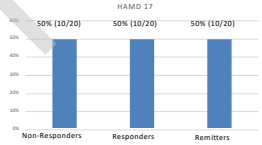
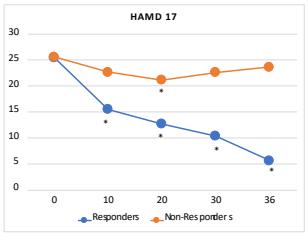
Individualized Targeting: Clinical Response



Failed medications in current episode: 7.06 (range 5-12)



*p<.05 from baseline

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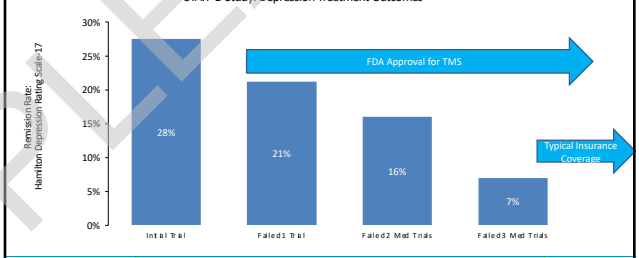
Why Consider TMS treatment for Depression?

STAR*D Study: Depression Treatment Outcomes



Likelihood of achieving remission drops with each subsequent medication trial

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

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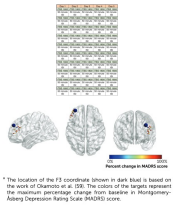
fcMRI-guided Accelerated TBS for MDD

Stanford Neuromodulation Therapy (SNT): A Double-Blind Randomized Controlled Trial

Protocol

- Accelerated iTBS (excitatory) to left DLPFC
- Individualized functional connectivity MRI target
- Pulse intensity: 90% vs 120% RMT
- 1800 pulses/session (**3x** 600pulses)
- **10** sessions per day (50min pause)
  - = 6 weeks of daily TBS
- 5 consecutive days (inpatient)
  - = 5 courses of TBS (30 weeks)



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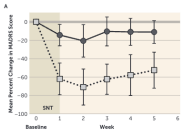
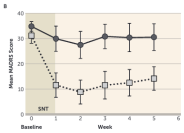
Accelerated TBS for MDD

Stanford Neuromodulation Therapy (SNT): A Double-Blind Randomized Controlled Trial





Active: 62.0%, 70.9%, 62.4%, 57.8%, 52.5%
Sham: 14.3%, 20.6%, 10.4%, 10.9%, 13.1%

Interim Analysis: 30 patients (aim was 60)
Cohen's d > 0.8 → Study ended

FDA cleared in 2022

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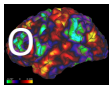
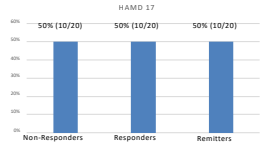
Individualized Targeting: Clinical Response





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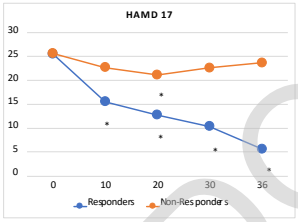

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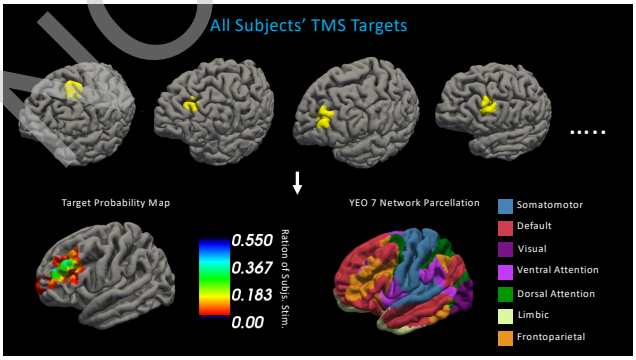

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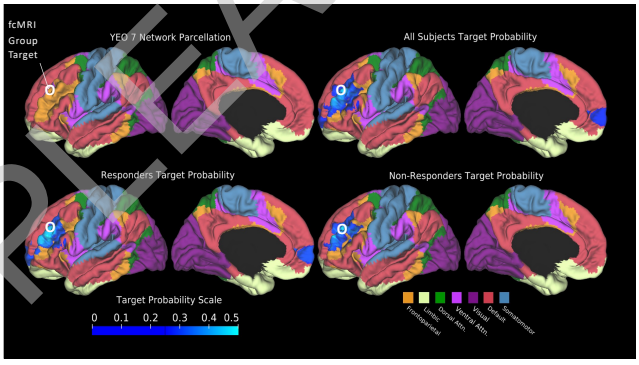

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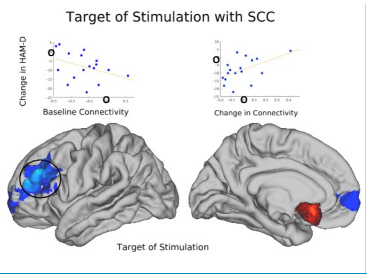
Node to Node effects



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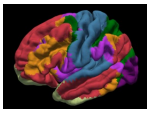
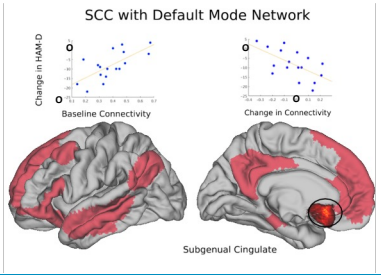
Node to Network Effects

- Somatomotor
- Default
- Visual
- Ventral Attention
- Dorsal Attention
- Limbic
- Frontoparietal





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Summary

- **Clinical Outcomes**
  - Individualized fcMRI-guided TMS leads to 50% response and remissions rate in highly treatment-resistant patients.
  - Much improved remission rate than standard TMS: seems to justify individualized vs. group target
  - All or nothing distribution: what are we missing in ⅓ patients?
- **Node to node (DLPFC to SGC) dynamics**
  - Weak baseline connectivity predicts greater response
  - Clinical response explained by strengthening of the anticorrelation
- **Node to Network dynamics**
  - Connectivity from the DLPFC target does not explain or predict clinical response
  - SGC connectivity to DMN predicts and explains response (distal effects)
    - Weak baseline positive correlations predict good response
    - Response is associated with strengthening of positive connectivity
  - Distal effects more important than local changes in the DLPFC target (network mechanism)

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