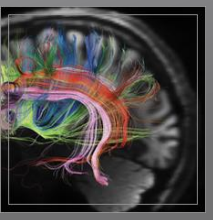



# NIMH Report: New Approaches to using Brain Stimulation in Depression


Bruce Luber, Ph.D.

*Staff Scientist*

*Noninvasive Neuromodulation Unit*
*Experimental Therapeutics and Pathophysiology Branch*
*National Institute of Mental Health*


National Institute of Mental Health

# Outline of Talk

- Depression as a Brain Disorder
- Subconvulsive stimulation:
  - Transcranial Magnetic Stimulation (TMS) as a Treatment and Research Tool for Depression
  - CPAS Approach towards TMS Research in Depression
- Convulsive stimulation:
  - Magnetic Seizure Therapy (MST)
  - Individualized Low Amplitude Seizure Therapy (iLAST)

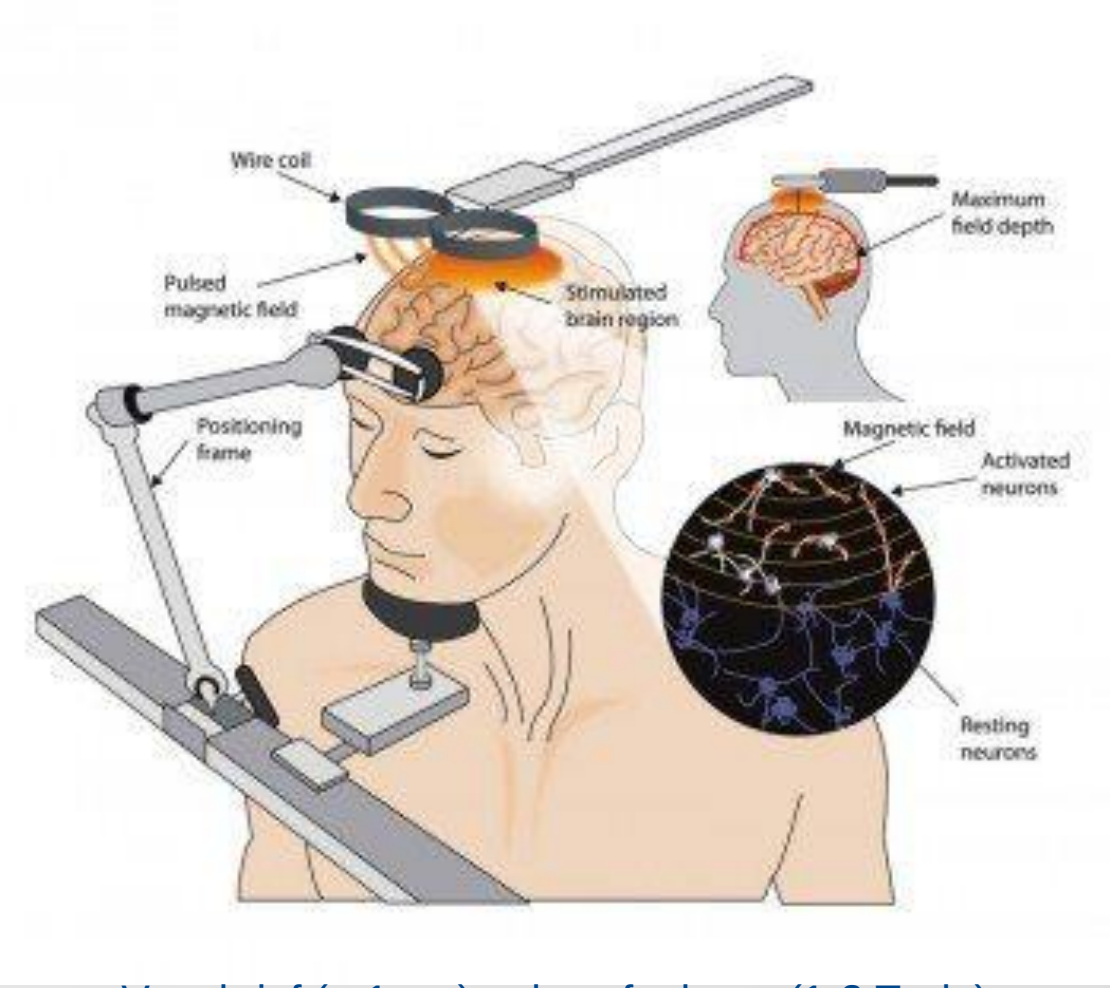
# Treatment Resistant Depression is a major health problem

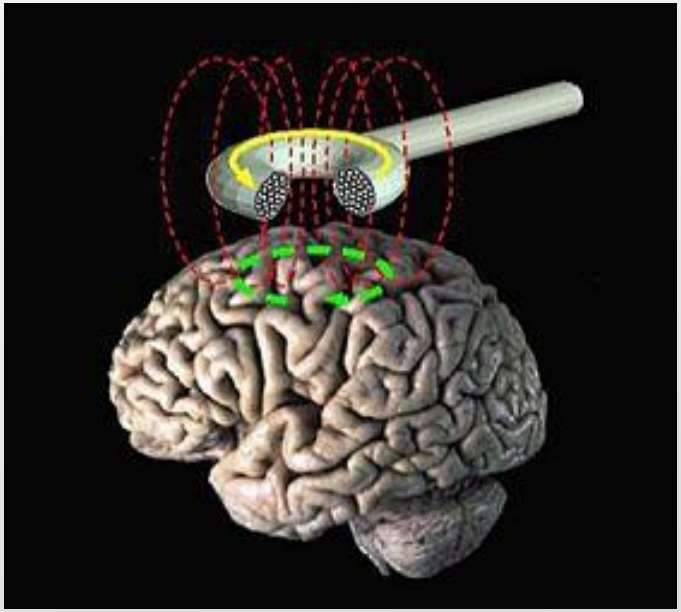
- Depression is a common mental disorder.
  - Globally, more than 300 million people of all ages suffer from depression.
    - -World Health Organization

- There is a great need for more effective treatments for depression:
  - For example, nearly one third of depressed patients achieve remission even after four consecutive trials of antidepressants
    - STAR*D trial, Warden et al., 2007

- Electromagnetic stimulation have proven their worth in treatment-resistant depression
  - Transcranial Magnetic Stimulation (TMS) was approved for use in treatment resistant depression in 2008
  - ECT remains the gold standard in treating depression

# Transcranial Magnetic Stimulation (TMS)

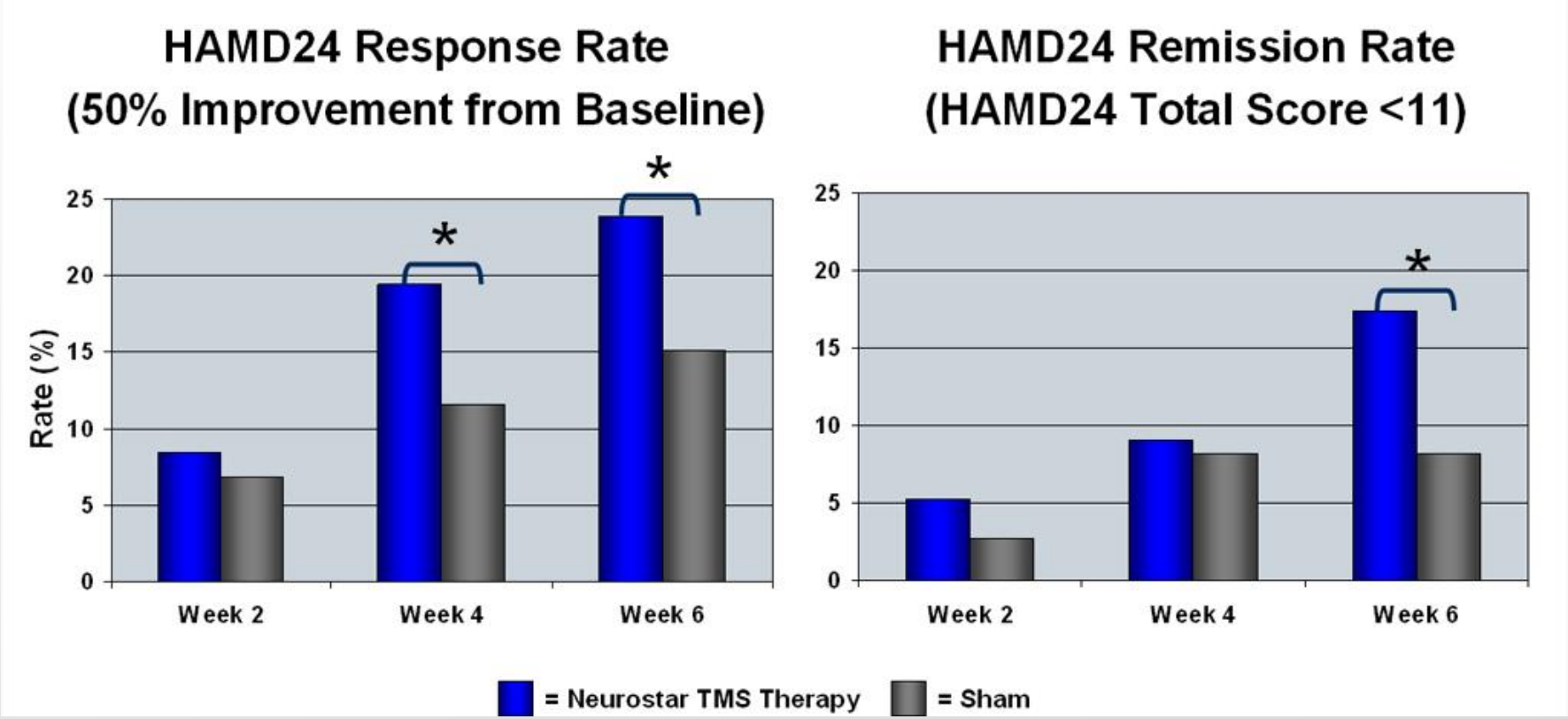


-Very brief (< 1 ms) pulse of a large (1-2 Tesla) magnetic field
-Changing magnetic field induces current flow in cortex near the coil
-Currents are large enough to set off action potentials in neurons

# TMS for Depression

- 2008: FDA Approved rTMS to treat Depression
- Though, like antidepressants, studies have shown modest effect sizes (15% remission, 30% response)




O'Reardon et al., 2007

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# Part of the reason for low efficacy in depression treatment may be in how TMS is targeted

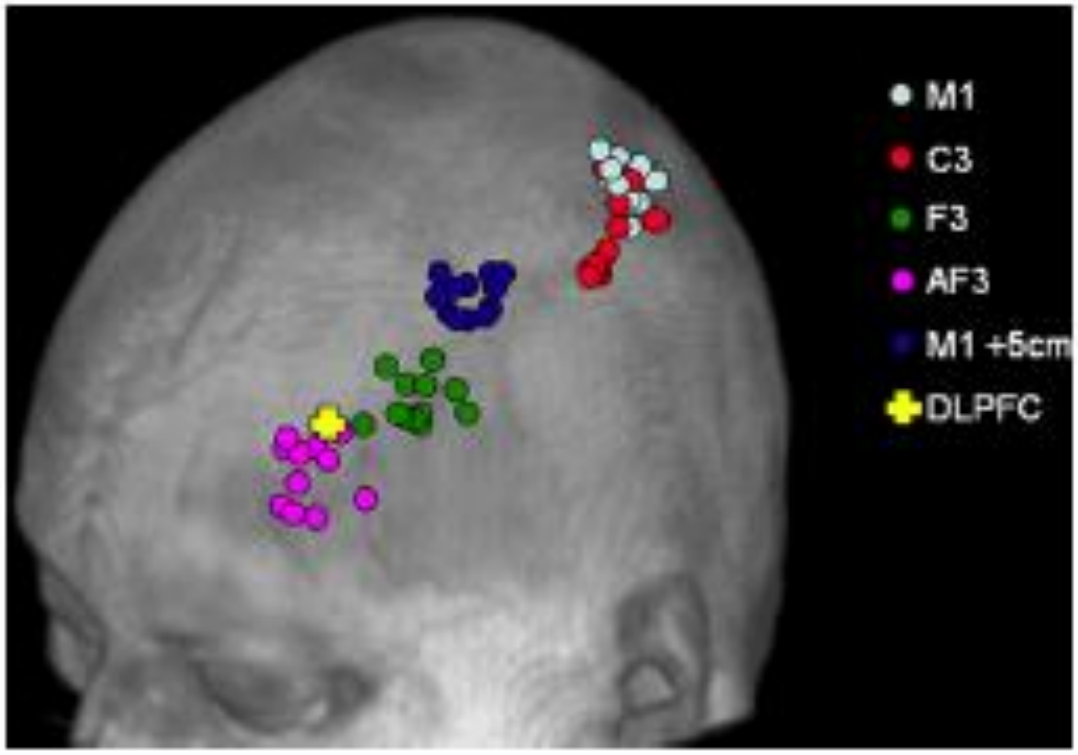



**Figure 1** Results of each subject's electrode positions relative to their left dorsolateral prefrontal cortex (DLPFC).

TMS is aimed at the dorsal lateral prefrontal cortex (DLPFC)

But its targeting is based on scalp localization:

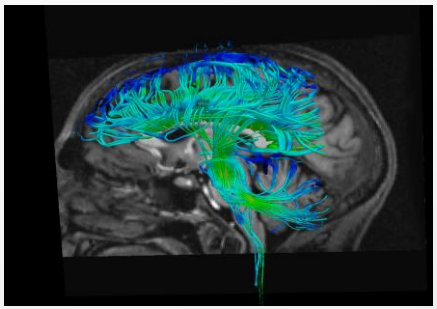
- -5 cm rule
- -10/20 EEG System

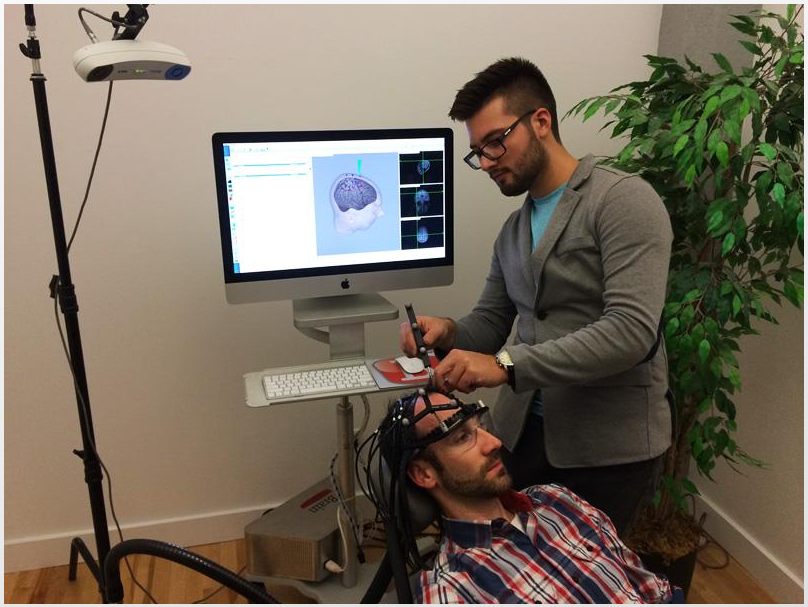
In both cases, only approximately place TMS coil over the DLPFC target

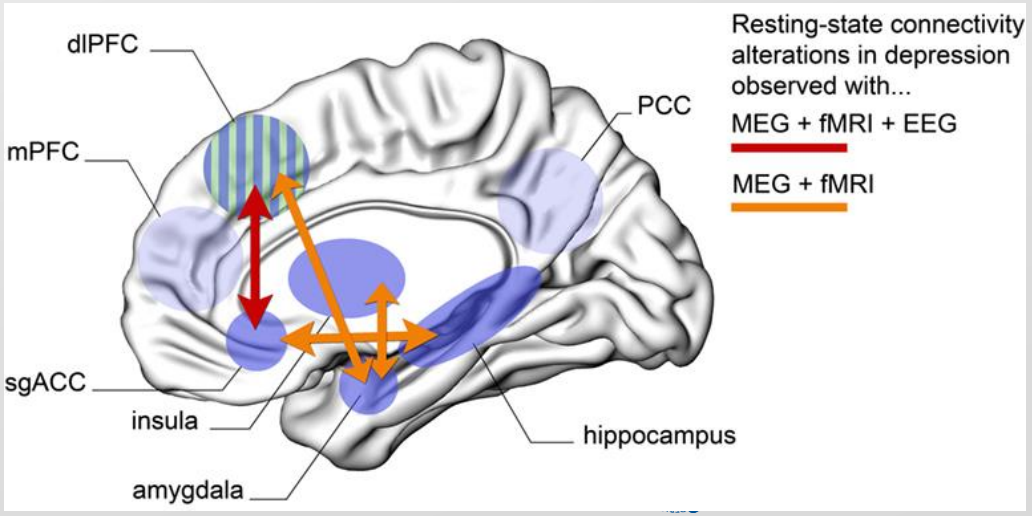
Fitzgerald et al
Brain Stim 2009

# There have been great advances in the tools to engage target brain networks

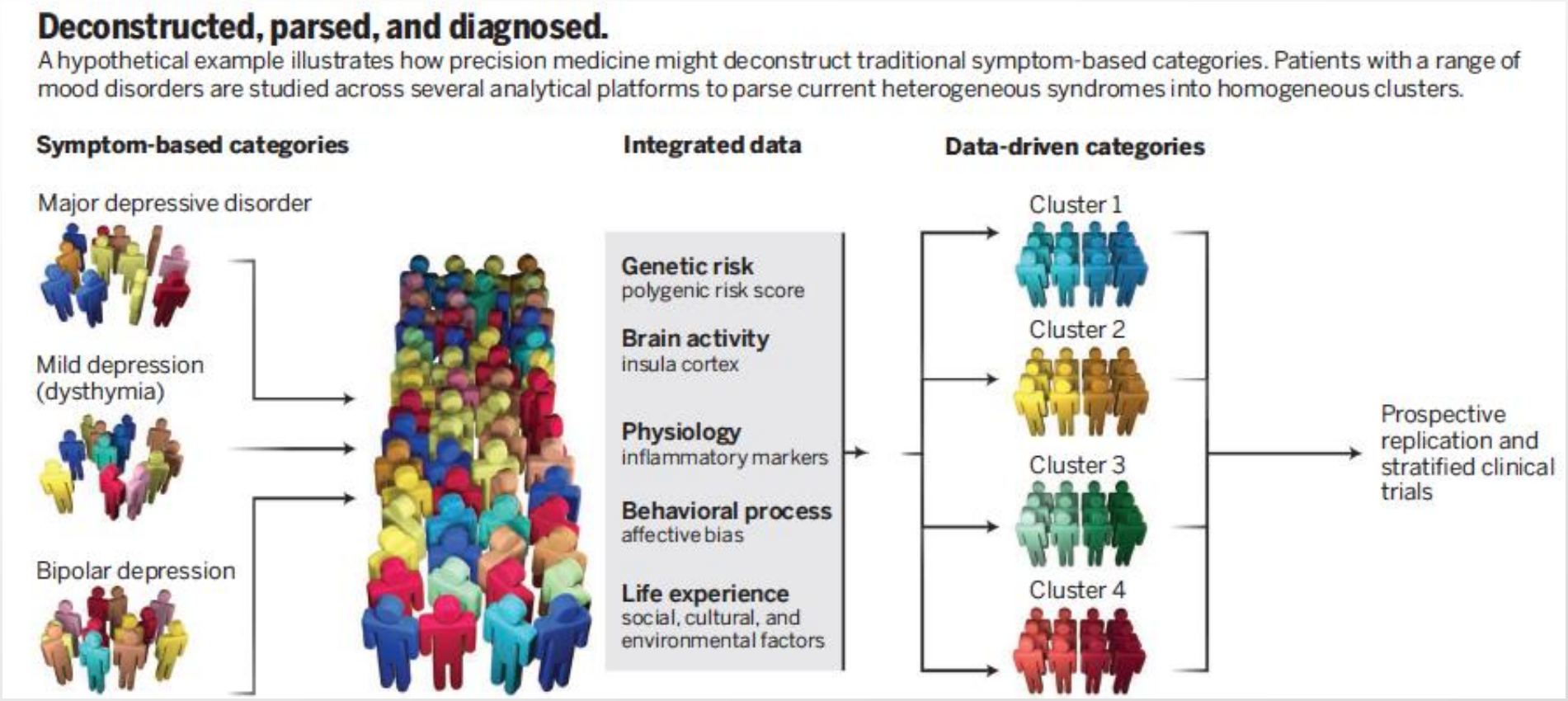
- Diffusion tensor imaging (DTI)
- fMRI and Resting State Connectivity
- Neuronavigation
- Electric field modeling
- Robotic coil holding
- Cortical targets
- Concurrent TMS/fMRI
- TMS/EEG (and soon, TMS/fMRI/EEG!)







# And there has been a fundamental change in how we think about depression:
# Research Domain Criteria (RDoC)




Taken from: Insel TR & Cuthbert BN. Brain Disorders? Precisely: Precision Medicine Comes to Psychiatry. Science. 2015 May 1;348(6234):499-500.

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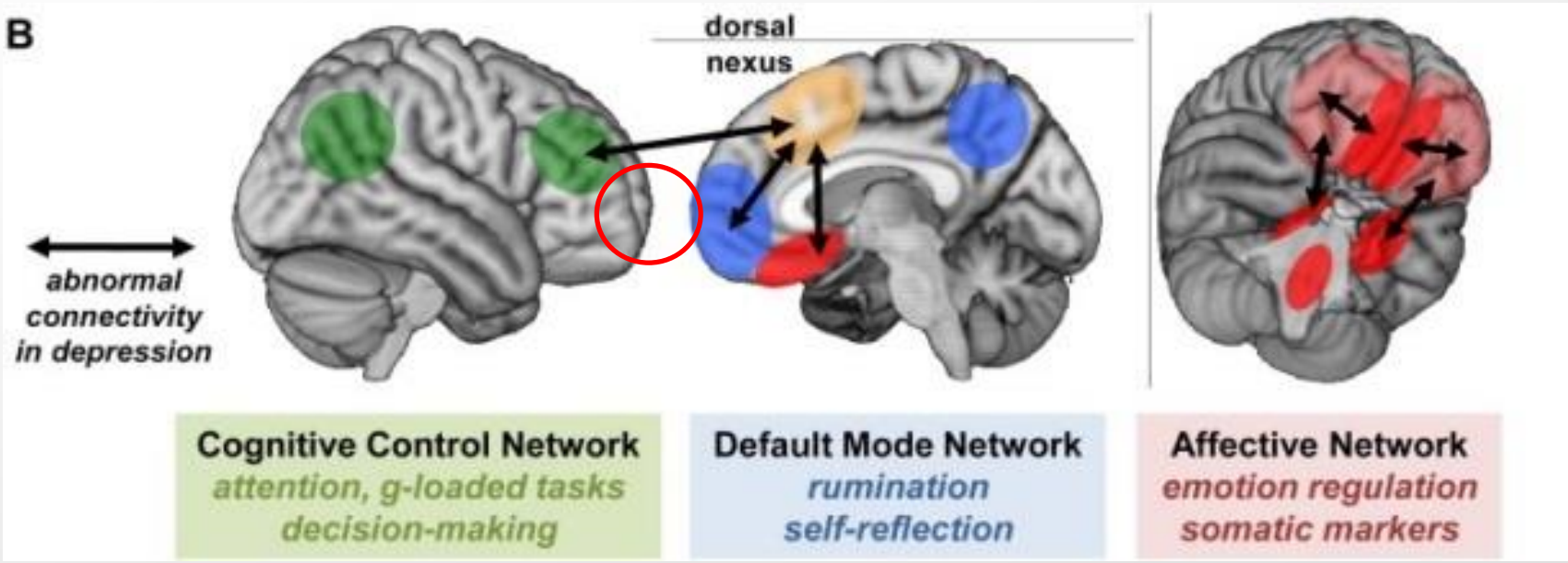
# “Depression” Networks as Targets

Example of functional networks involved in depression:



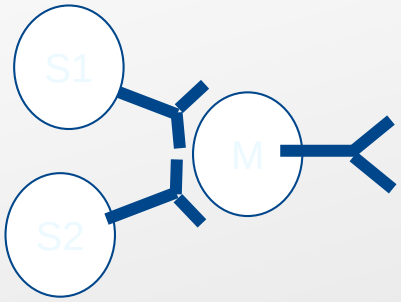

Downar & Daskalakis, 2013

Can we use TMS to modulate abnormal activity in these brain networks?

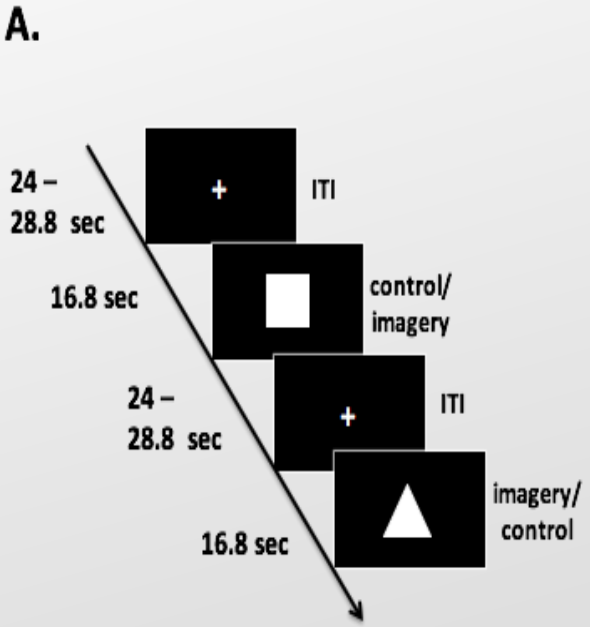
# Functional targeting: A novel tool to engage and modulate brain networks

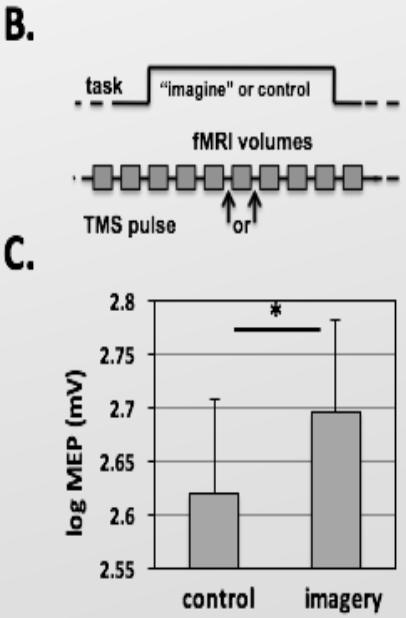
- There is a huge source of variability in stimulation: the TMS pulse interacts with whatever activity is ongoing at the target

- But active contraction and imagery experiments in motor cortex show that controlling the state of the brain may be more effective




Synaptic coincidence: Hebbian plasticity




Further, activating the neurons in the target that are of interest gives them an edge for firing

Repeated pairings of local functional activity and TMS pulses may create a cumulative synaptic change along Hebbian lines

Luber et al., in preparation

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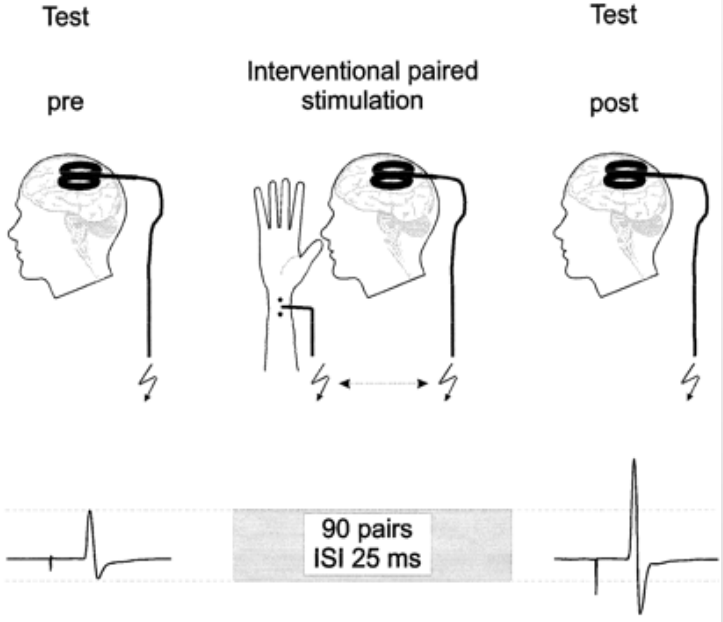
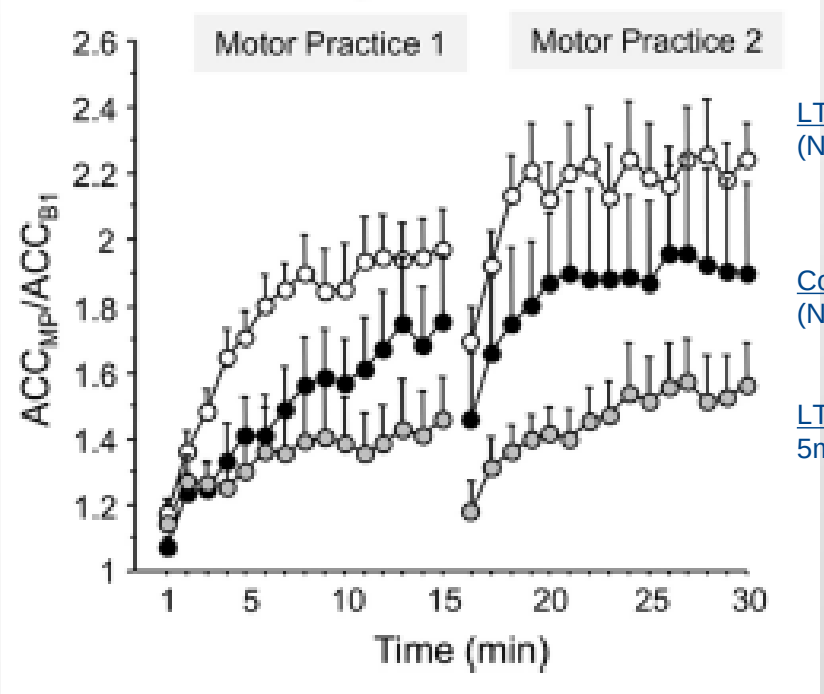
# Most elementary form of functional targeting: Paired Associate Stimulation (PAS)

## Long-lasting enhancements: creating long-term potentiation (LTP)/ long-term depression (LTD)-like plasticity effects

Paired Associated Stimulation (PAS)




LTP PAS (N20+2ms)

Control PAS (N20+100 ms)

LTD PAS (N20-5ms)

PAS stimulation increases effectiveness (accuracy in a motor task), in a cumulative way

Stefan et al. 2000; Ridding et al. 2001

Ziemann 2009 J Neurosci 29: 5597-5604

# Generalizing PAS:
# CPAS: Cognitive paired associate stimulation

Generalizing PAS in the motor cortex to any brain function and network suggests **Cognitive PAS (CPAS)**:

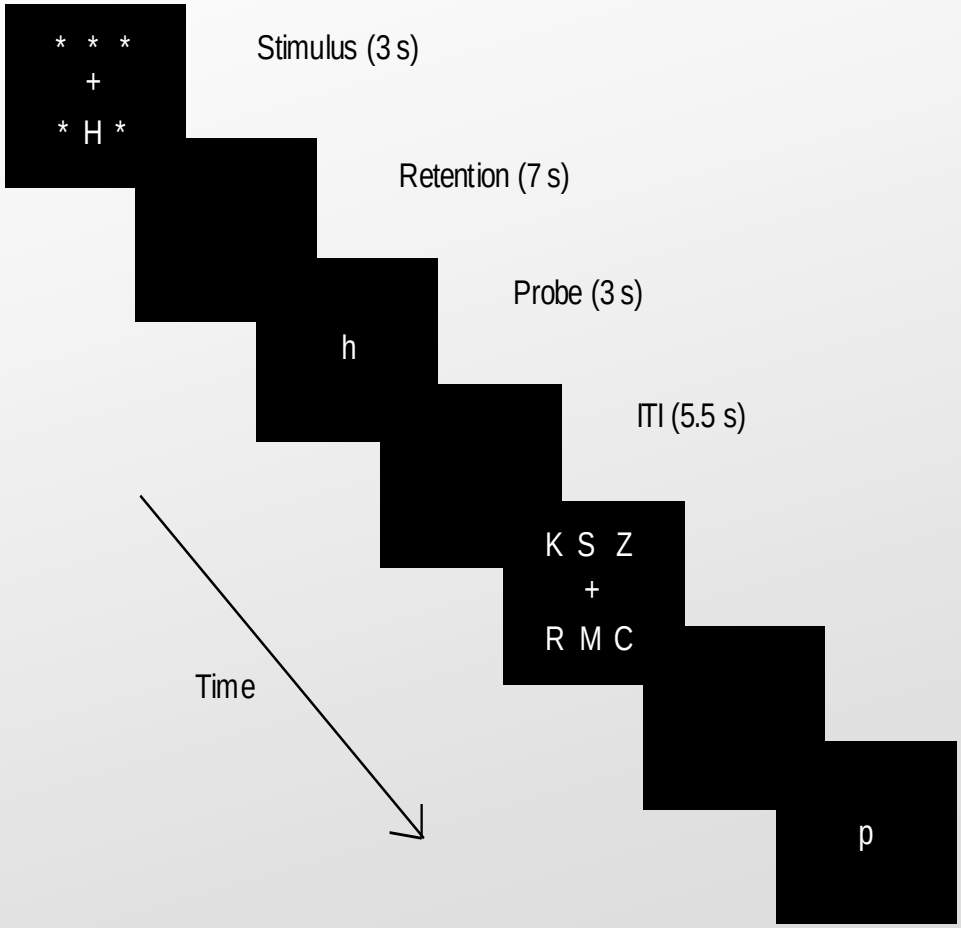
- a more active approach of **functional targeting**:
  - simultaneous activation of a network with noninvasive brain stimulation and behavioral performance

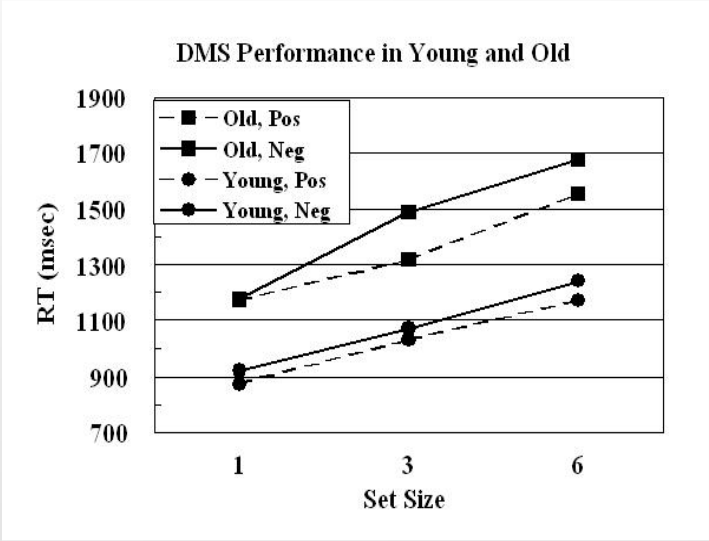
A paradigm for using CPAS in treating cognitive deficits:

- - a multi-modal approach to stimulation: concurrent TMS and task performance to enhance plasticity changes in targeted functions
- - repeated sessions to create a cumulative effect in those plasticity changes

# An example of using the CPAS paradigm to remediate a cognitive deficit

## Working Memory (WM) Task

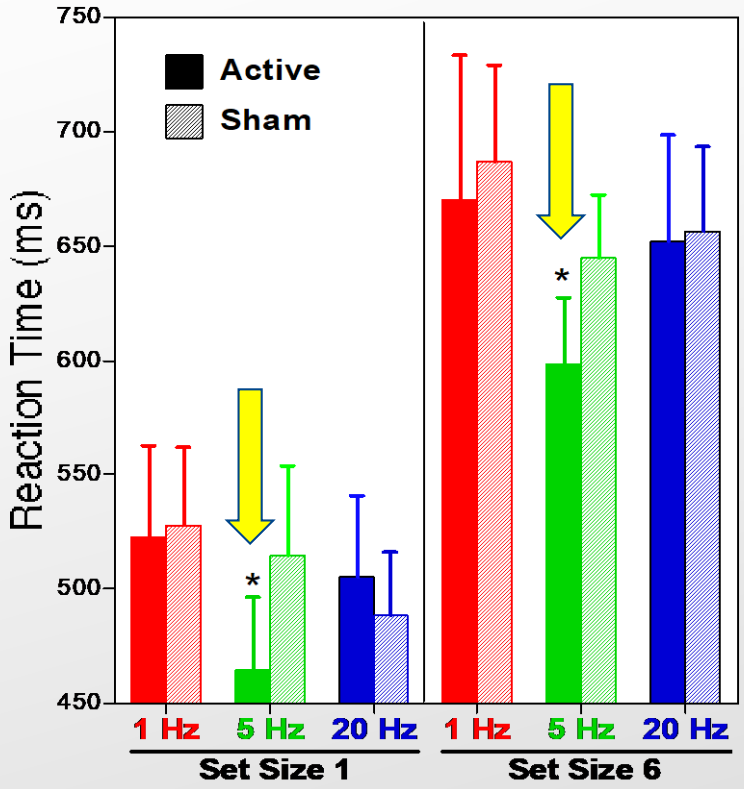


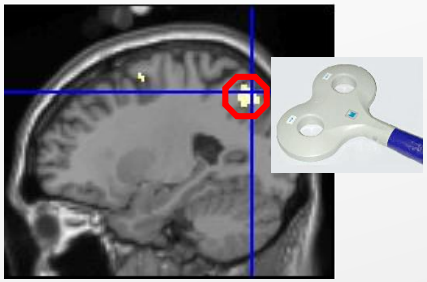




In collaboration with
Yaakov Stern

National Institute of Mental Health

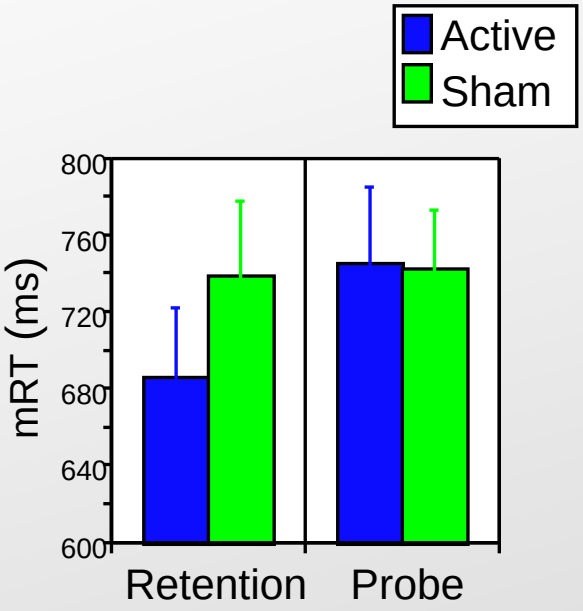
# First step:
# Demonstrate TMS enhancement of working memory



Site specific effect:
Parietal but not DLPFC

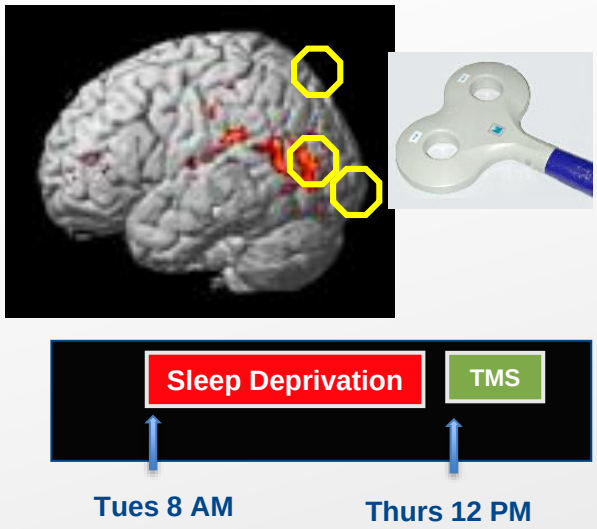
Frequency specific effect:
5 Hz rTMS during the retention phase reduced reaction time (RT) for set size 1 and 6 ($p<0.01$).

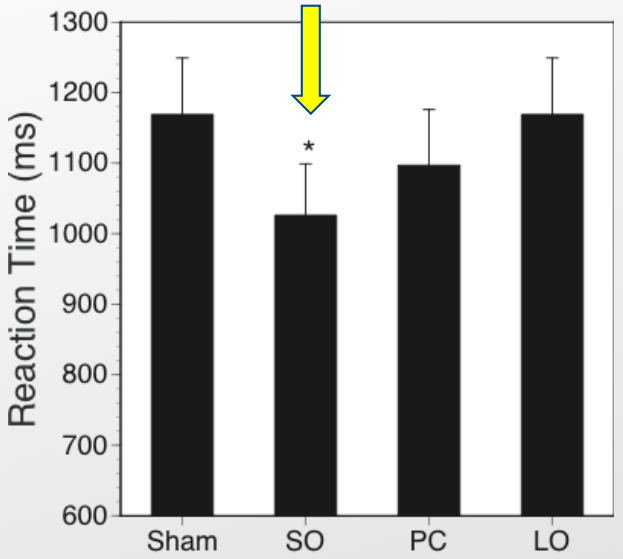


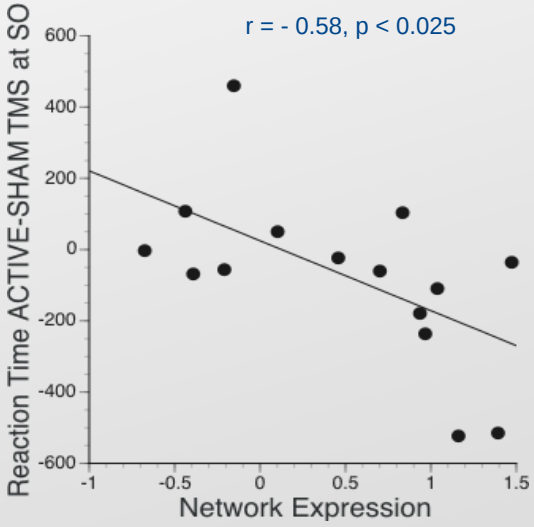

Task Phase specific effect:
With a new group (N=22), 5Hz to mPar reduced RT only during retention period

Luber et al Brain Research 2007;1128:120-129

# Second Step:
# Demonstrate engagement of a brain network associated with a working memory deficit




- Mapped network associated with resilience to sleep deprivation (N=15)
- TMS to resilience targets during task
- Site-specific enhancement found with TMS applied to lateral occipital cortex
- Degree of improvement correlated with network expression

Luber et al. Cereb. Cortex 2008;18:2077-85

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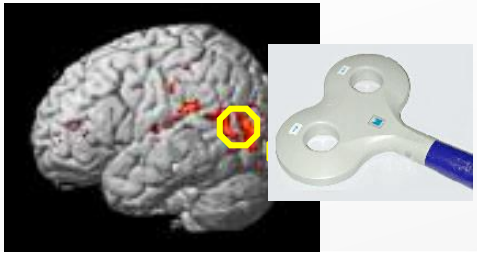
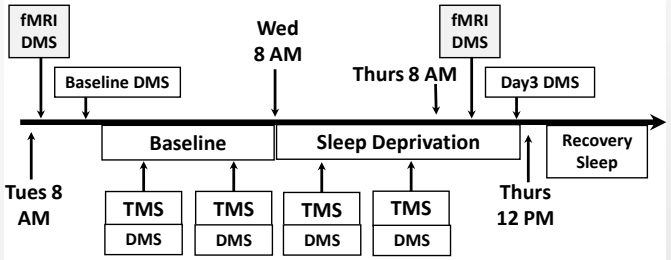
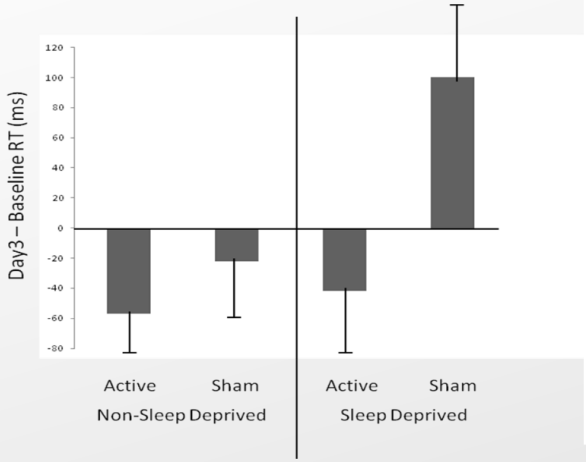
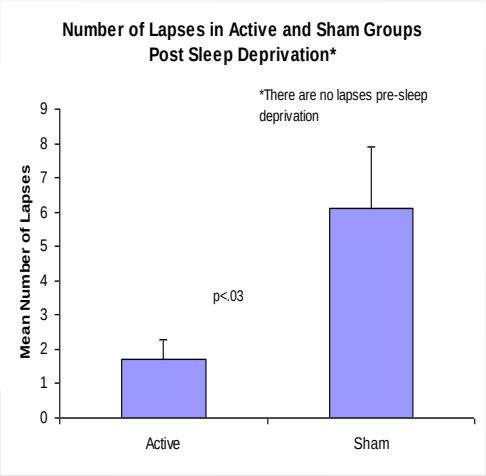
# Third Step:
# Long-lasting prevention of memory deficit due to sleep deprivation

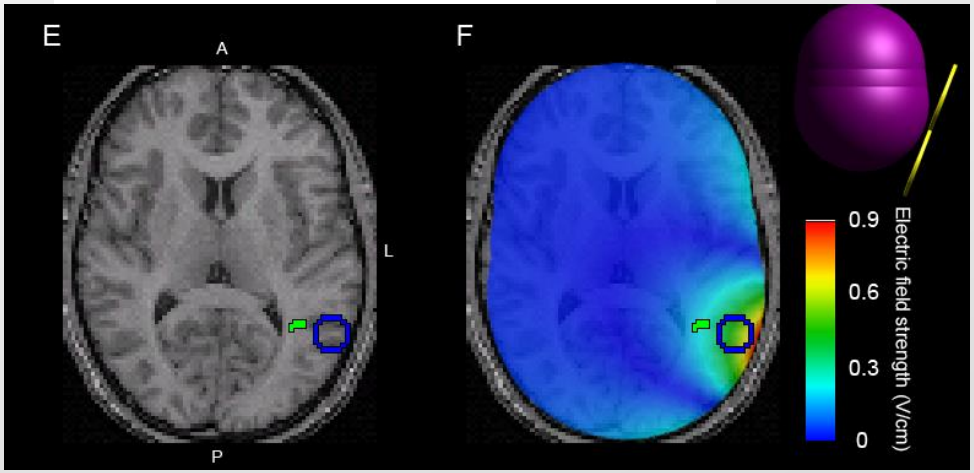





Post – Pre fMRI difference in RT between Active and Sham groups




Luber et al Sleep 2013;36:857-71

5 Hz TMS+Task to lateral occipital cortex (LOC) (2/day x 2 days)
Prevented slowing and memory lapses **a full 18 hrs** after the last TMS

Change in fMRI network localized under TMS coil

Currently applying to age-related WM deficits

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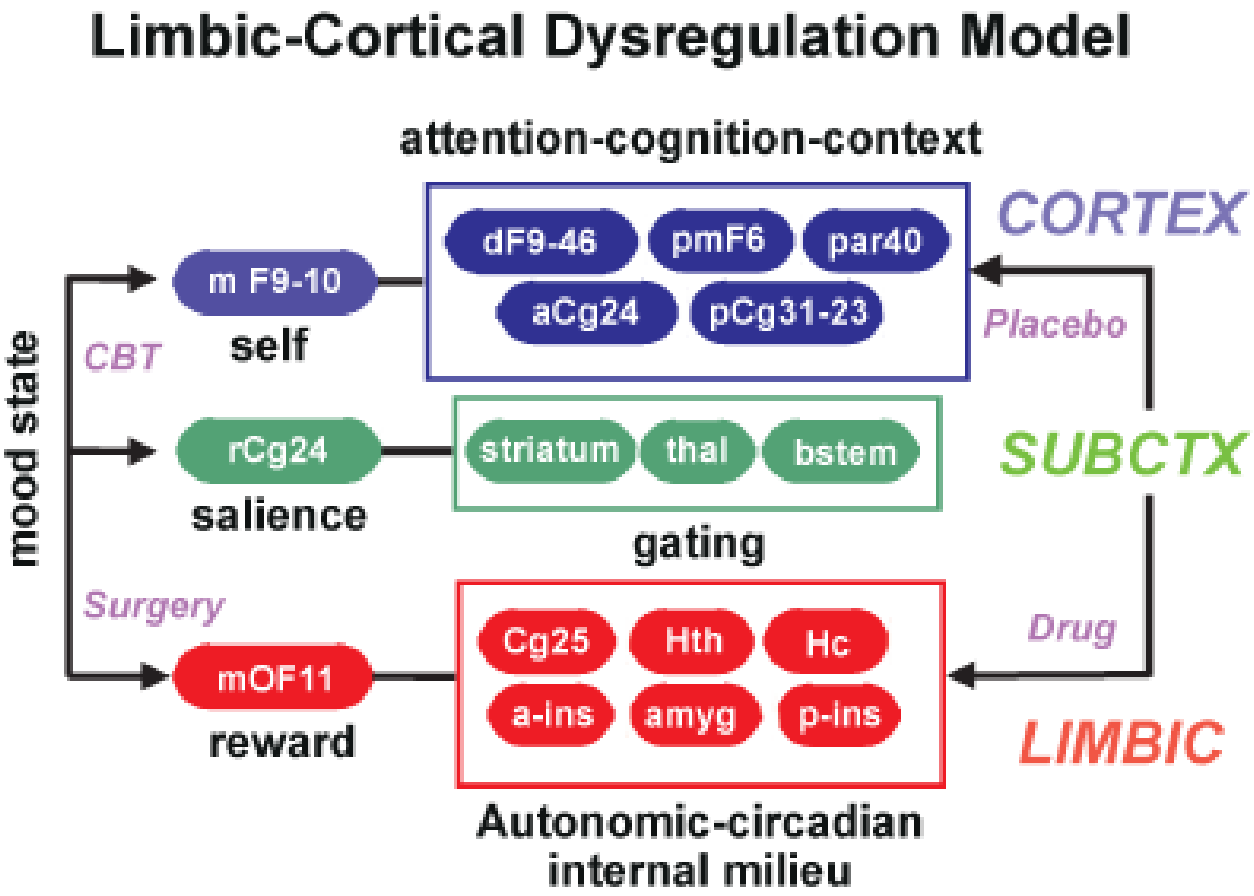
# Back to Depression: Imaging studies have mapped out “depression” networks to engage




One problem has been finding a “task” that activates this network

Mayberg et al., 2003

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# Social-cognitive systems for self-regulation: Regulatory Focus Theory
## *Promotion* and *prevention* systems

| Approach | Avoidance |
| --- | --- |
| Positive Valence System | Negative Valence System |
| **At cortical level:** | |
| **Promotion goals** | **Prevention goals** |
| *Promotion*: strategic bias toward attaining positive end-states by "making good things happen" | *Prevention*: strategic bias toward attaining positive end-states by "keeping bad things from happening" |
| Disorder in promotion system: possible pathway to depression? | Prevention success leads to quiescence; prevention failure is associated with anxiety |

# Goal Priming Task

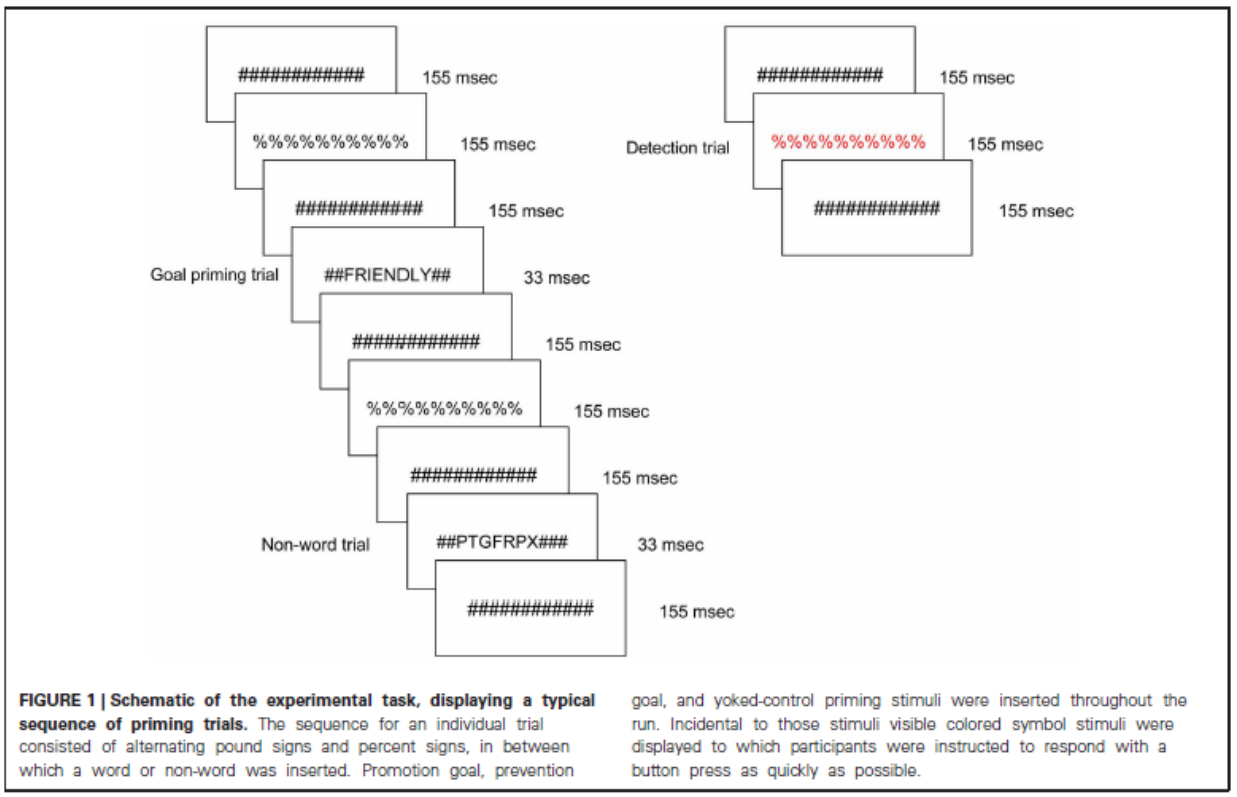



**FIGURE 1 | Schematic of the experimental task, displaying a typical sequence of priming trials.** The sequence for an individual trial consisted of alternating pound signs and percent signs, in between which a word or non-word was inserted. Promotion goal, prevention goal, and yoked-control priming stimuli were inserted throughout the run. Incidental to those stimuli visible colored symbol stimuli were displayed to which participants were instructed to respond with a button press as quickly as possible.

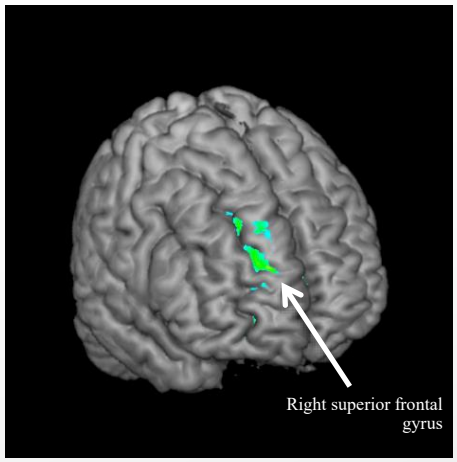
Participants complete computerized version of the *Selves Questionnaire* (SQ; Higgins, Bond, Klein, & Strauman, 1986) sampling participants' own promotion and prevention goals

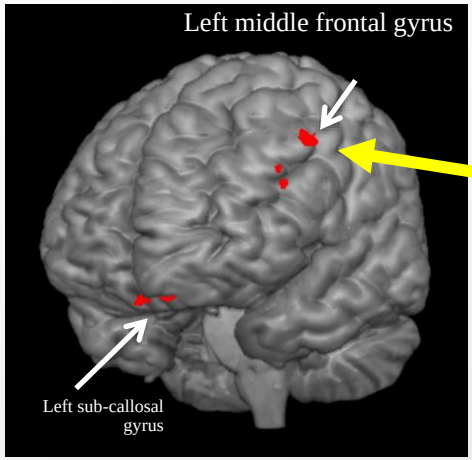
These promotion and prevention goal words are presented, along with control words subliminally during the task

3 runs, each 600 s long:
In each run, spaced around 18 s:
16 promotion words
16 prevention words
16 control words

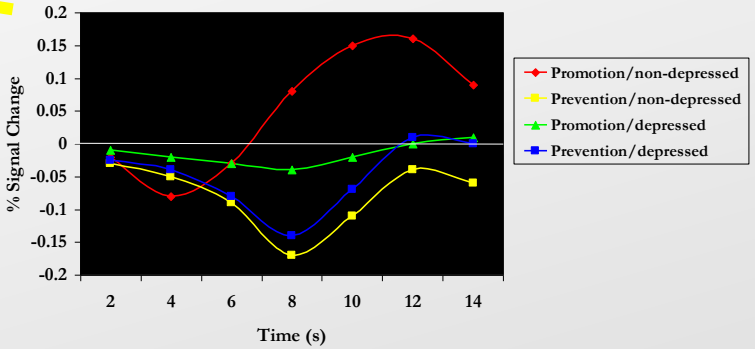
Strauman et al., 2013

# Network associated with promotion/prevention



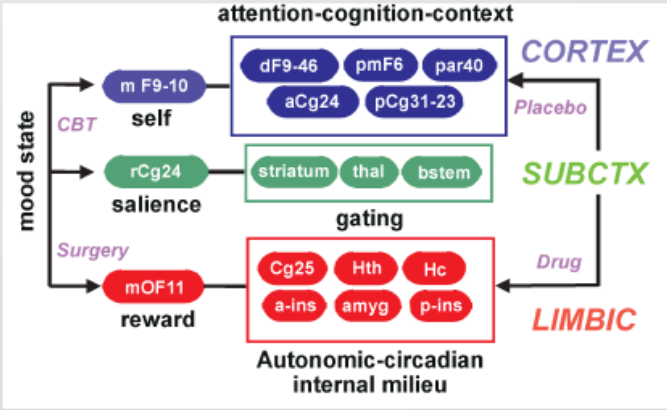

Signal change over time showing left prefrontal cortex (PFC) activation



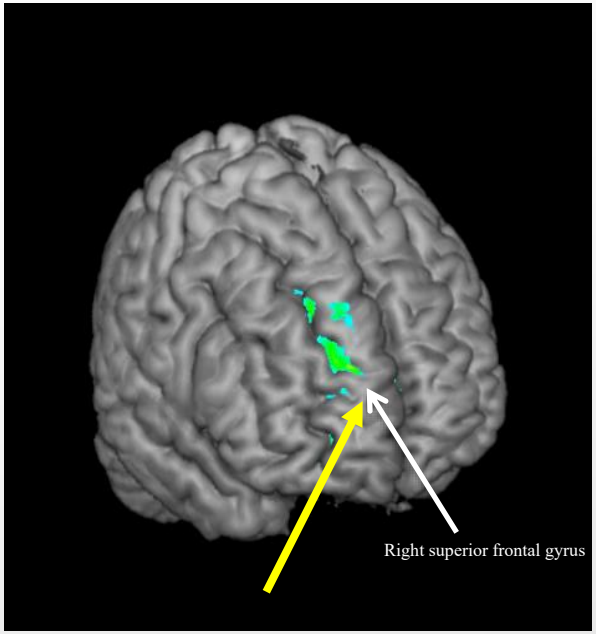

Results from a Group (CTL, DEP) X Priming Type (promotion, prevention priming) conjunction analysis. From Detloff et al., (under review).

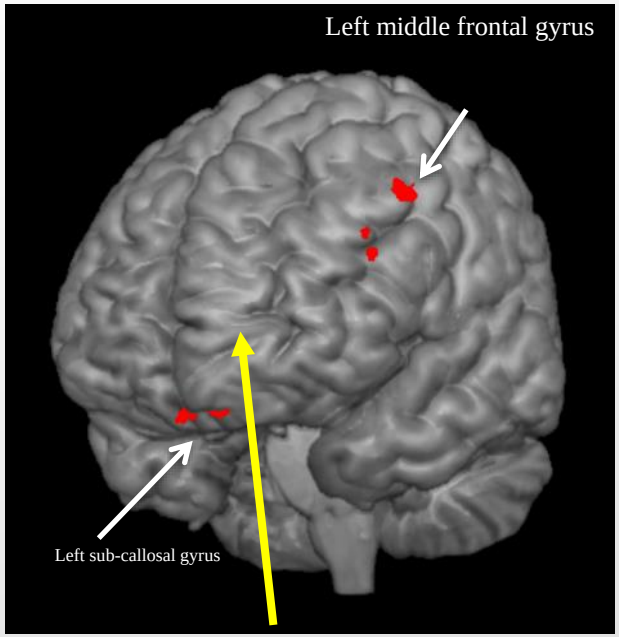
Prevention failure: Depressed pts with comorbid GAD showed *increased right* PFC activation following prevention priming: Hyperactivation associated with vigilance and anxiety

Promotion failure: *decreased left* PFC activation: Hypoactivation associated with dysphoria and anhedonia



# Relationship of Promotion/Prevention imaging results with TMS depression paradigms




Disturbances in Prevention goals (comorbid anxiety) related to hyperactivation

1 Hz (inhibitory) TMS to right DLPFC effective

Disturbances on Promotion goals (depression) related to hypoactivation

10 Hz (excitatory) TMS to right DLPFC effective

Detloff et al., (under review)

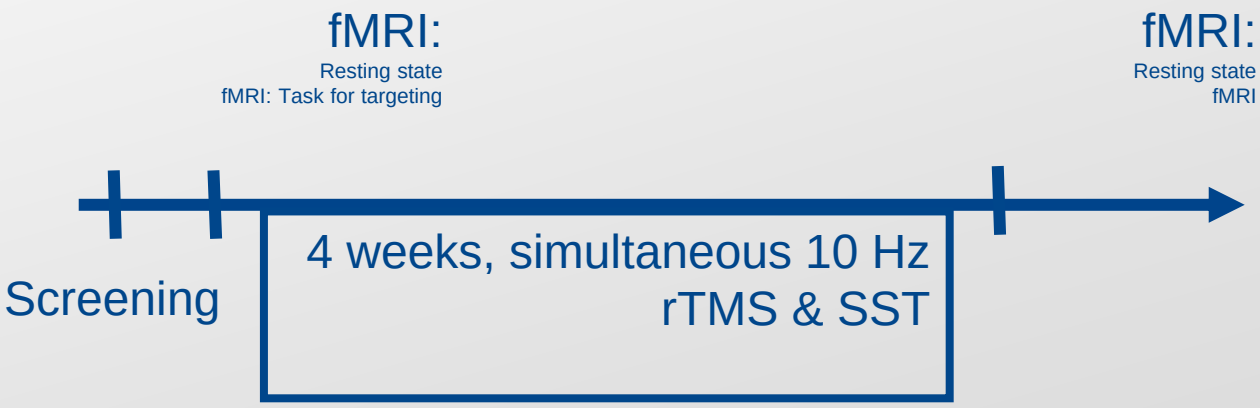
# A CPAS-Based TMS depression treatment

- A depression-related network including cortical areas involved in emotional regulation, can be engaged
  - These regions include left and right prefrontal cortex regions where TMS has caused clinical response in depression, but which can be targeted with precision on an individual basis
- Functional targeting can be achieved by applying TMS simultaneously with talk therapy
  - For example, by using a structured, skill-based therapy for depression similar to cognitive therapy (CT) developed by Strauman et al.
  - This therapy has been shown to affect the same DLPFC area as the fMRI targeting task:
    - Baseline fMRI differences between med-free patients (N=10) and controls disappeared post therapeutic course (16 sessions): Strauman, Smith & Eddington, 2017

# Pilot study: The CPAS approach to Depression

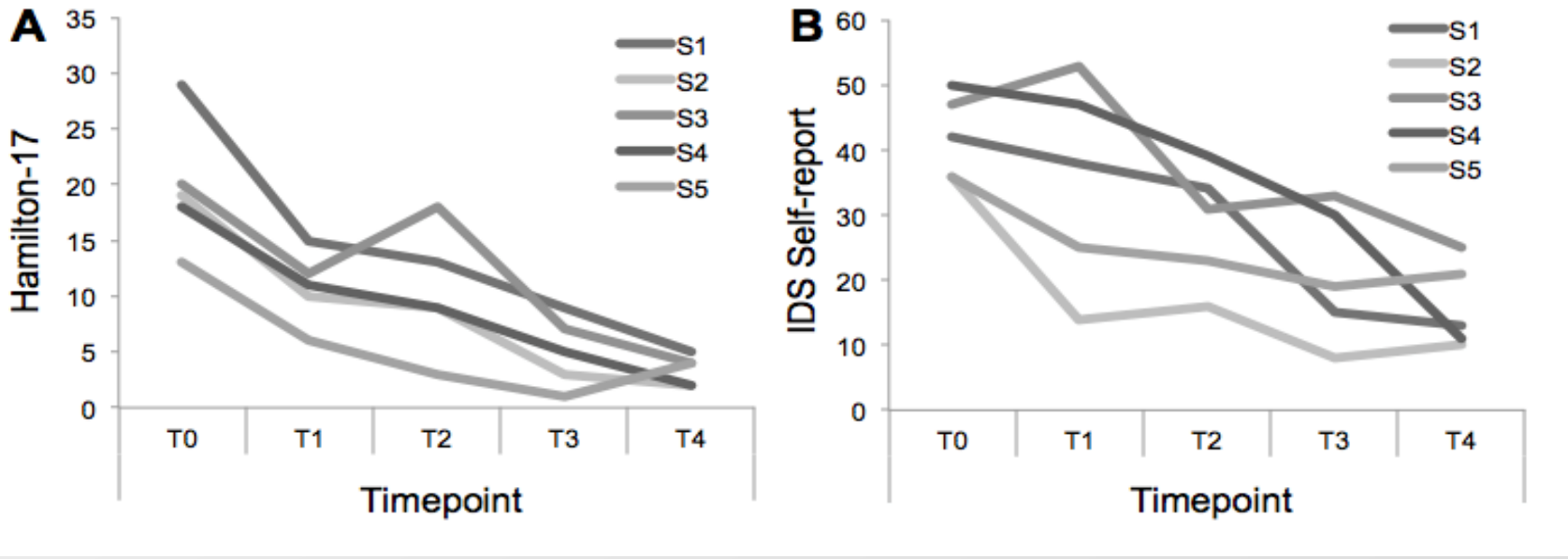
Pilot experiment (open label, 5 treatment-resistant MDD patients)

- Individualized targeting: left PFC promotion region activated in fMRI by priming task
- Plasticity component: simultaneous Self System Therapy (SST) with rTMS (standard parameters)



# The CPAS approach to Depression

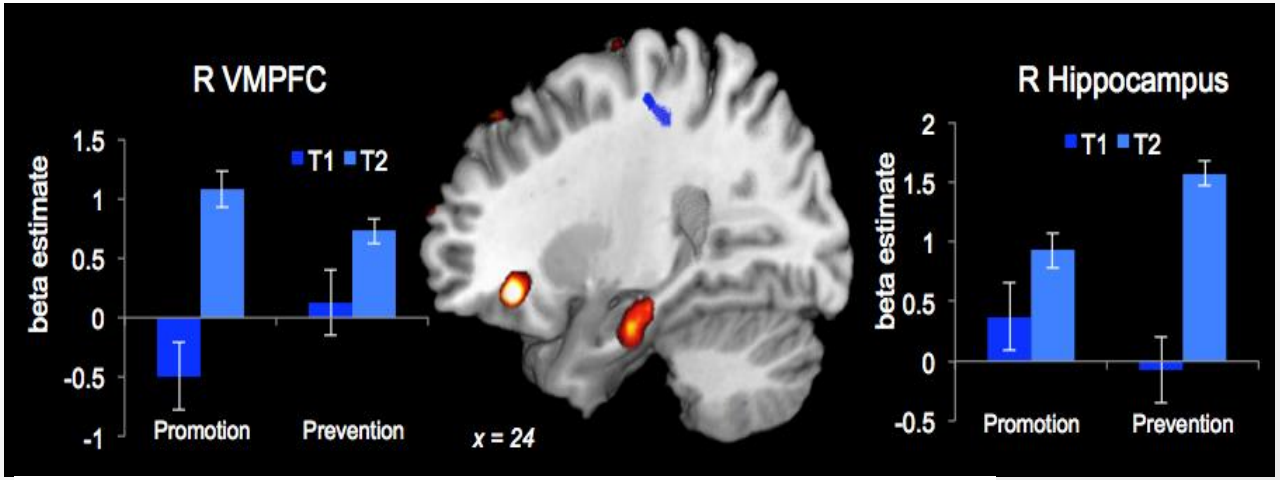
## By 4 weeks, all 5 patients remitted

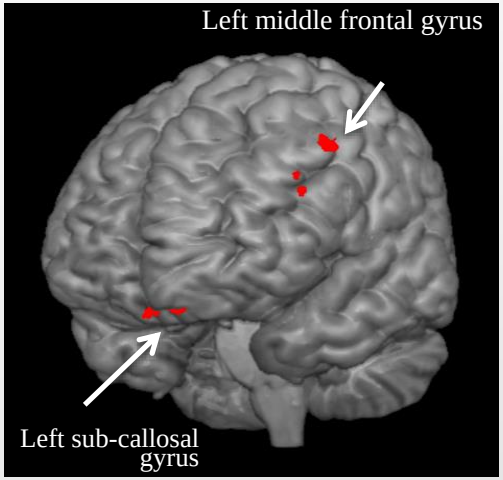


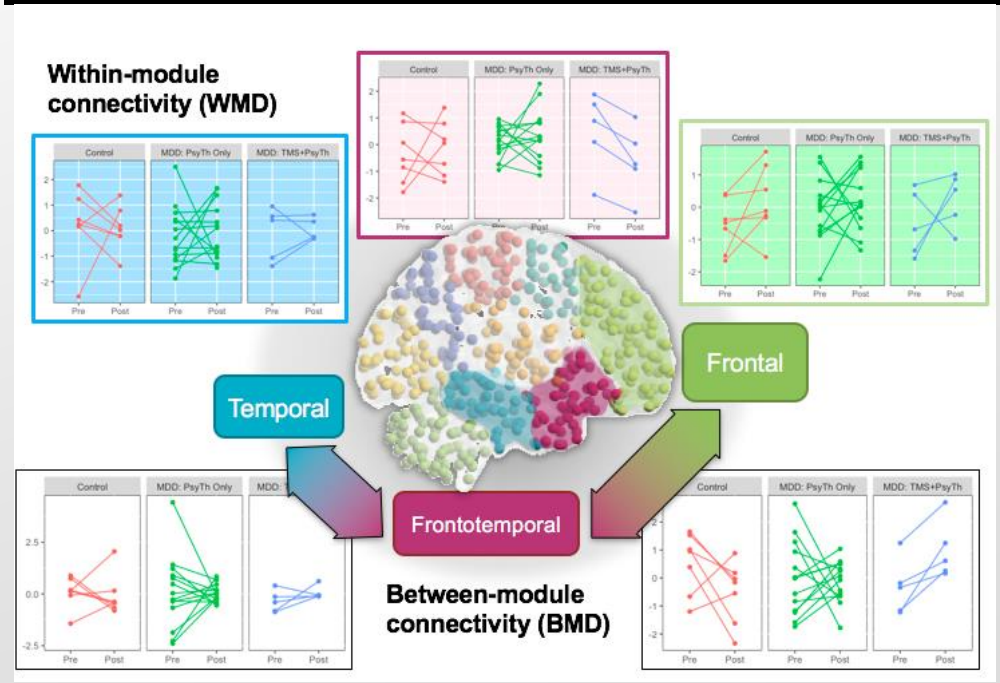

$HAMD_{17}$ total scores (A) and IDS Self report scores (B) for five patients suffering from major depressive episode, from the initial visit (T01), and at weekly follow-up assessments; tests administered before treatment.

Neacsiu et al., in press

# Group analysis of pre/post fMRI differences showed changes in regions of the ”Depression Network"




Functional activation changes from pre- to post-TMS course. Strongest effects are present in Ventro-medial PFC, a site of clear focus for targeted depression therapies. Warm colors: T2 > T1; cool colors: T1 > T2; results displayed at $p < 0.005$, uncorrected.

Neacsiu et al., in press

Graph-theoretical analysis showed a significant increase in fronto-temporal connectivity compared with healthy volunteers and patients who received only therapy

Davis et al., in revision

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# New TMS/therapy Study:
# A CPAS Approach to TMS Depression Treatment

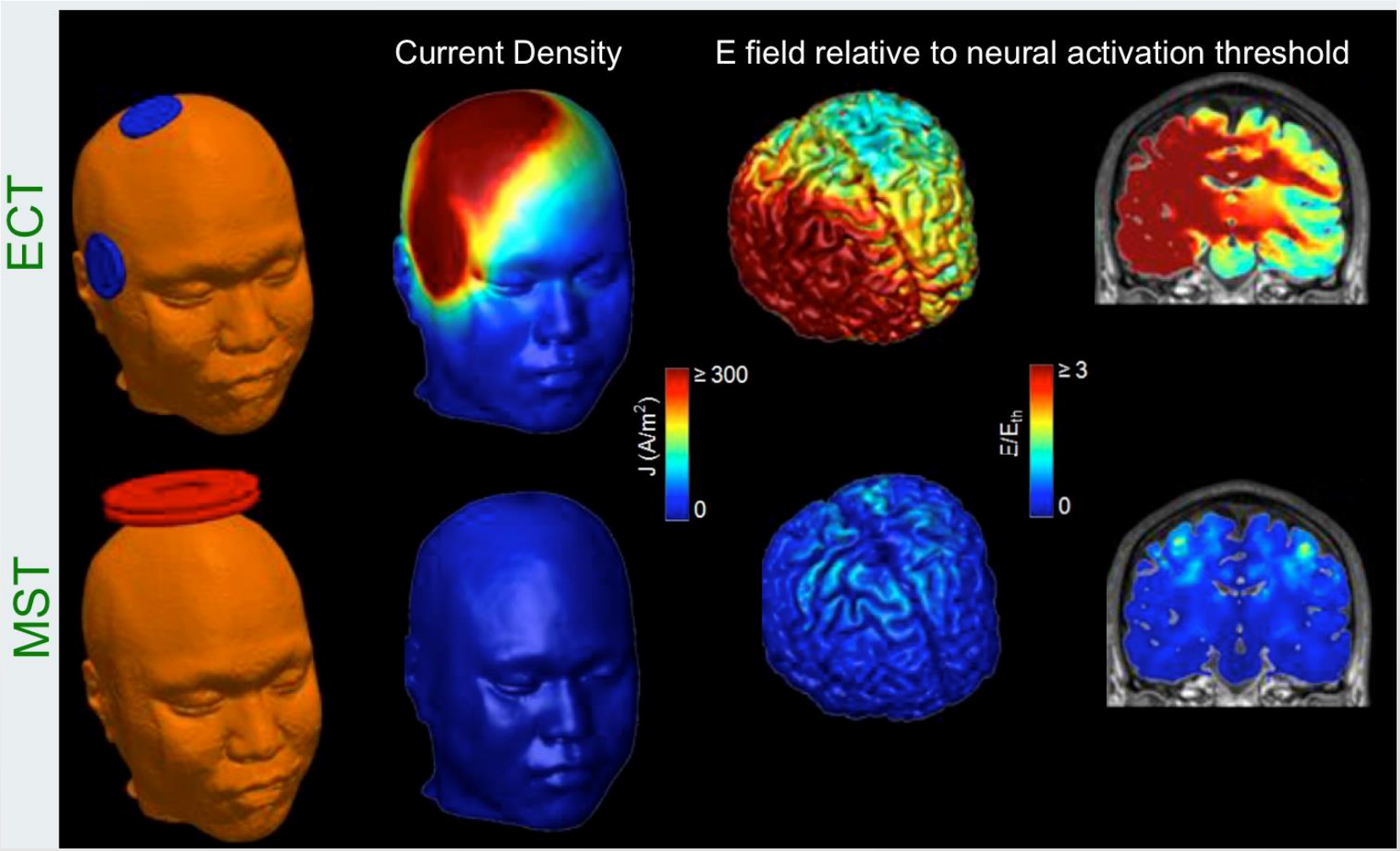
- The CPAS approach- engaging specific brain networks associated with targeted psychological functions using functional neuroimaging, noninvasive brain stimulation, and functional targeting- may result in increased efficacy of neuropsychiatric treatment.

- We have begun a larger clinical trial to test our CPAS approach

  - comparing depressed individuals receiving either active or sham TMS
  - enrolling eligible adults ages 18-65 with major depressive disorder, who are free of other serious medical conditions.
  - If you are currently taking anti-depressants, you may still be eligible.
  - This inpatient and/or outpatient study involves daily visits for 8 weeks followed by once-monthly visits for 3 months.
  - for more information email moodresearch@mail.nih.gov or call 1-877-MIND-NIH (1-877-646-3644)

NIH National Institute of Mental Health

# Convulsive Treatment of Depression: Magnetic Seizure Therapy (MST)




MST produces more localized, lower-intensity electrical stimulation in the brain

# MST seizures are lower in amplitude compared to ECT

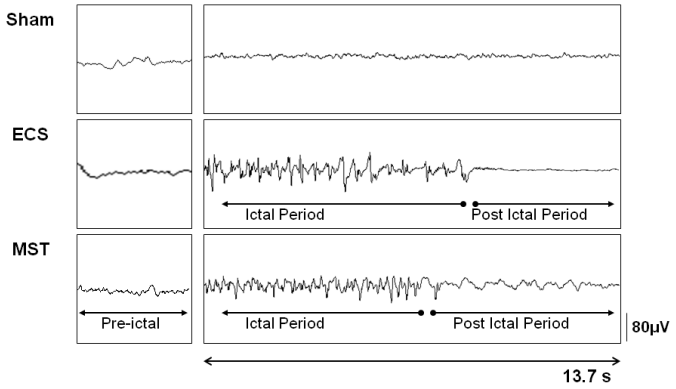
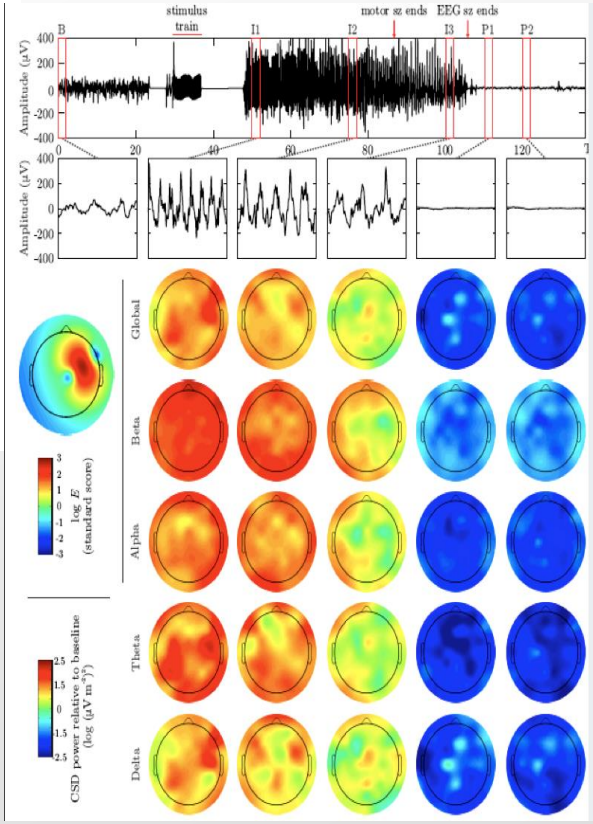
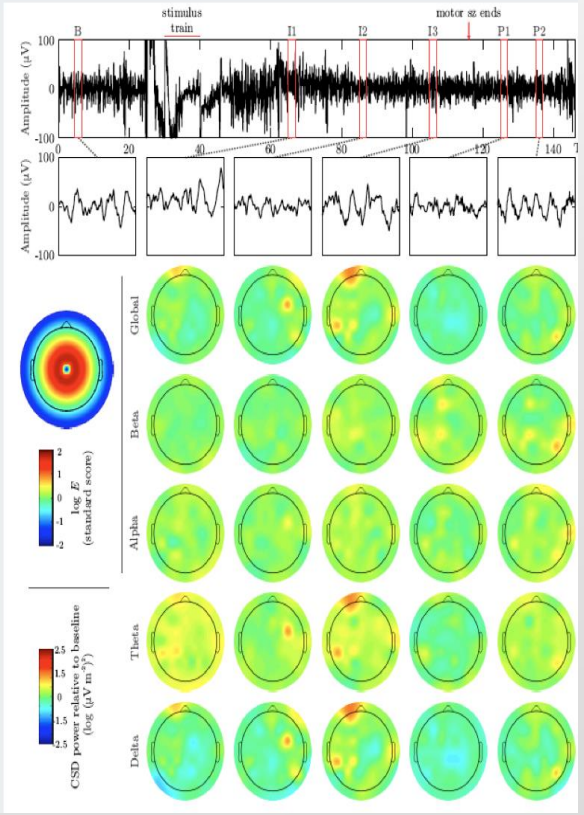



Figure 1




Cycowicz, Rowny, Luber, Lisanby 2014 J ECT

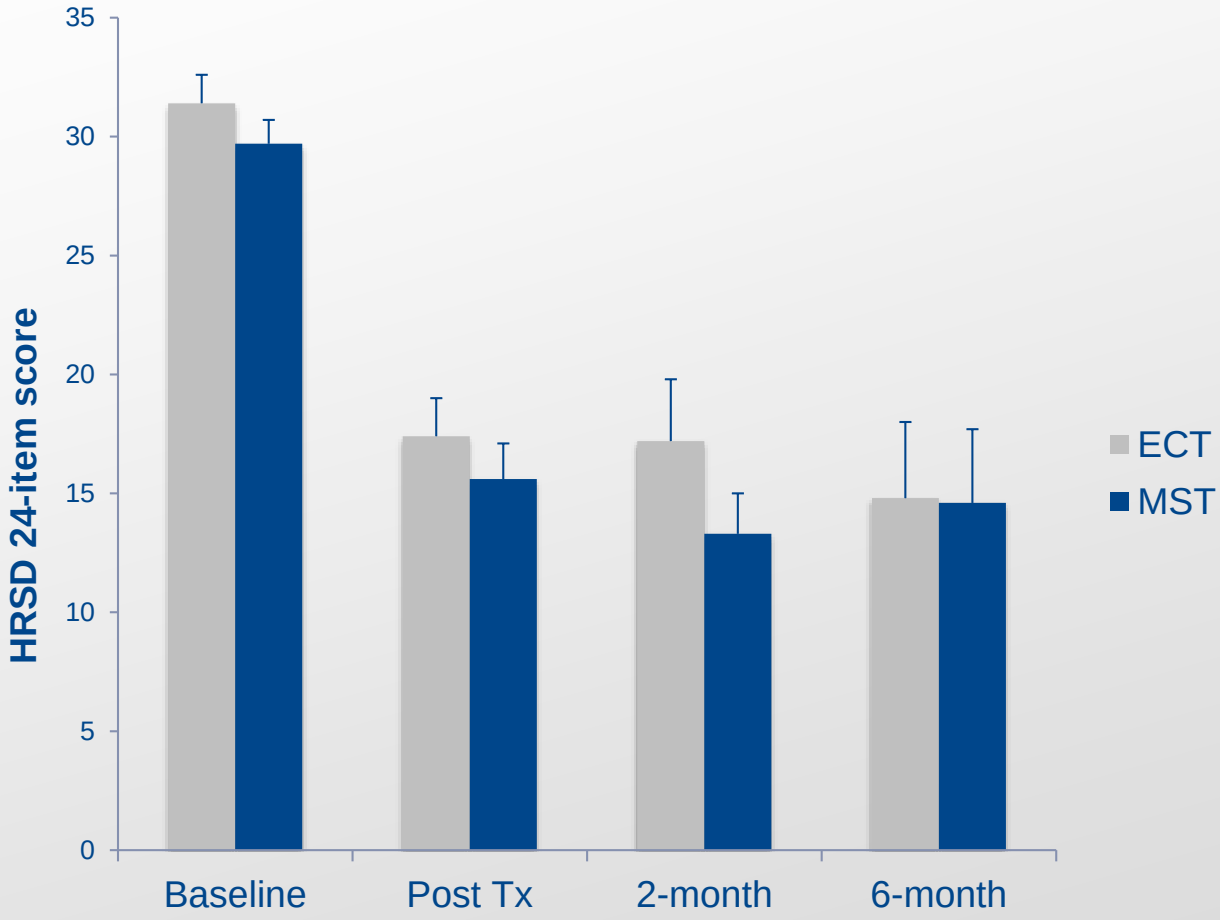
# Comparing ECT and MST head-to-head

**Table 1. Comparison of patient demographics between MST and ECT groups.**

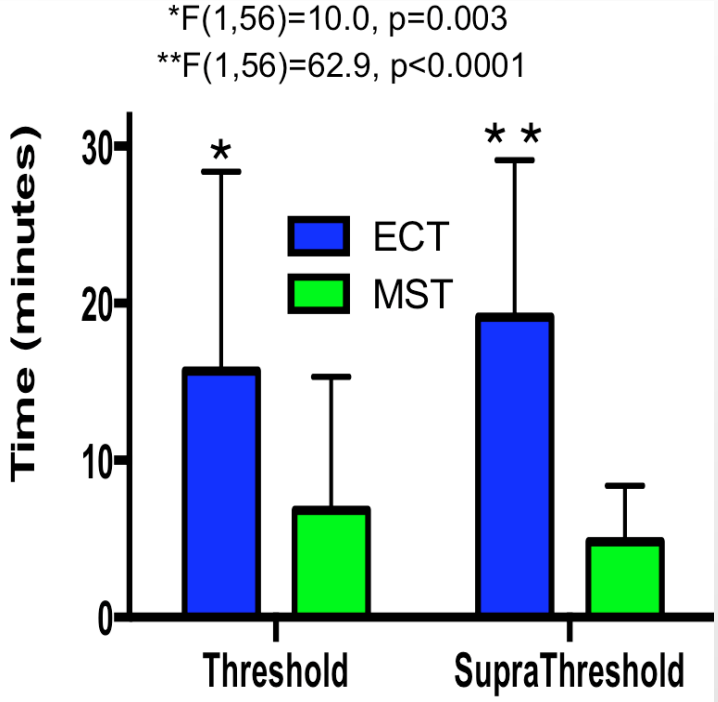
| | Patient Group | |
|---|---|---|
| | ECT | MST |
| N | 37 | 34 |
| Mean Age | 48.1 ± 13.0 | 47.7 ± 14.7 |
| Gender (M:F) | 17:20 | 13:21 |
| Years of Education | 15.5 ± 2.5 | 16.3 ± 3.2 |
| N, Uni- or Bi-polar | 6 | 5 |
| Baseline HRSD | 31.4 ± 7.3 | 29.7 ± 6.1 |
| Mean duration, current Episode (weeks) | 138 ± 150 | 134 ± 220 |

Luber et al., in preparation

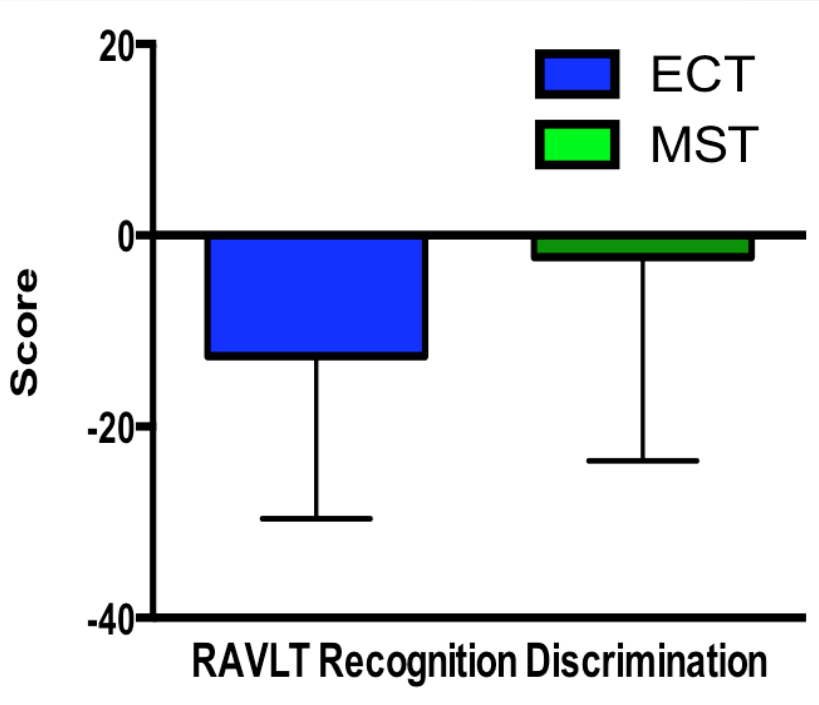
# ECT and MST produced similar drops in depression severity



# MST led to faster re-orientation and lower cognitive effects than ECT

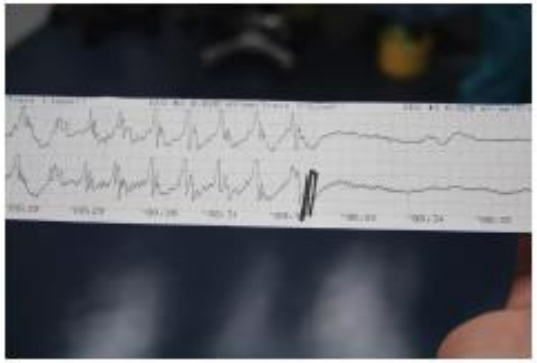
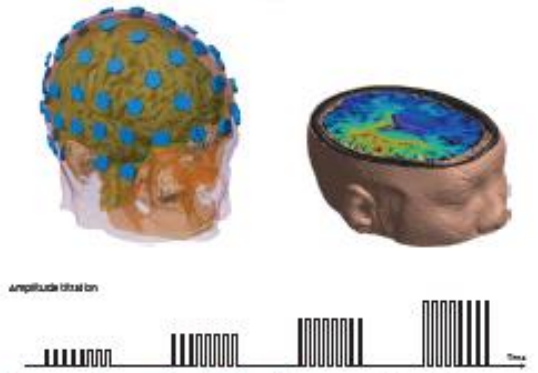
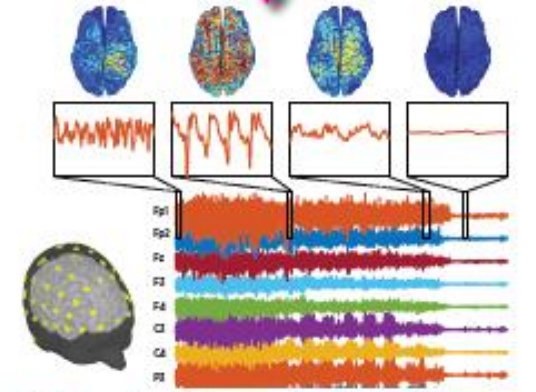



Faster reorientation time following MST than ECT, with both threshold and suprathreshold treatments.




Improved verbal memory on the Rey Auditory and Verbal Learning Test (RAVLT) following MST compared to ECT.

# Individualized Low Amplitude Seizure Therapy: Reinventing ECT

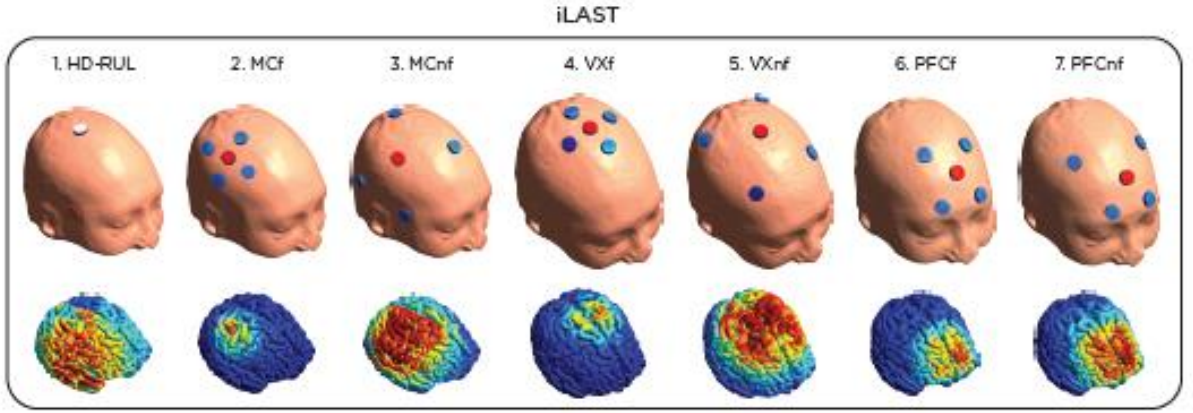
| | 1 stimulus dosing | 2 spatial targeting | 3 seizure topography |
|---|---|---|---|
| Conventional ECT |  |  |  |
| | § uses too high amplitude current<br>§ does not account for interindividual differences in head anatomy or cortical excitability | § two large disc electrodes spaced wide apart<br>§ produces broad, nonfocal stimulation, contributing to side effects | § two frontal EEG channels<br>§ no spatial information about the seizure |
| iLAST |  |  |  |
| | § current amplitude titration coupled with individual computation head model<br>§ minimizes over-stimulation<br>§ reduces interindividual variability | § multielectrode array allows flexible and focal targeting of specific brain regions | § high density ictal recording allows discovery of optimal seizure propagation pattern |

# iLAST: First-in-human trial, Fall 2018

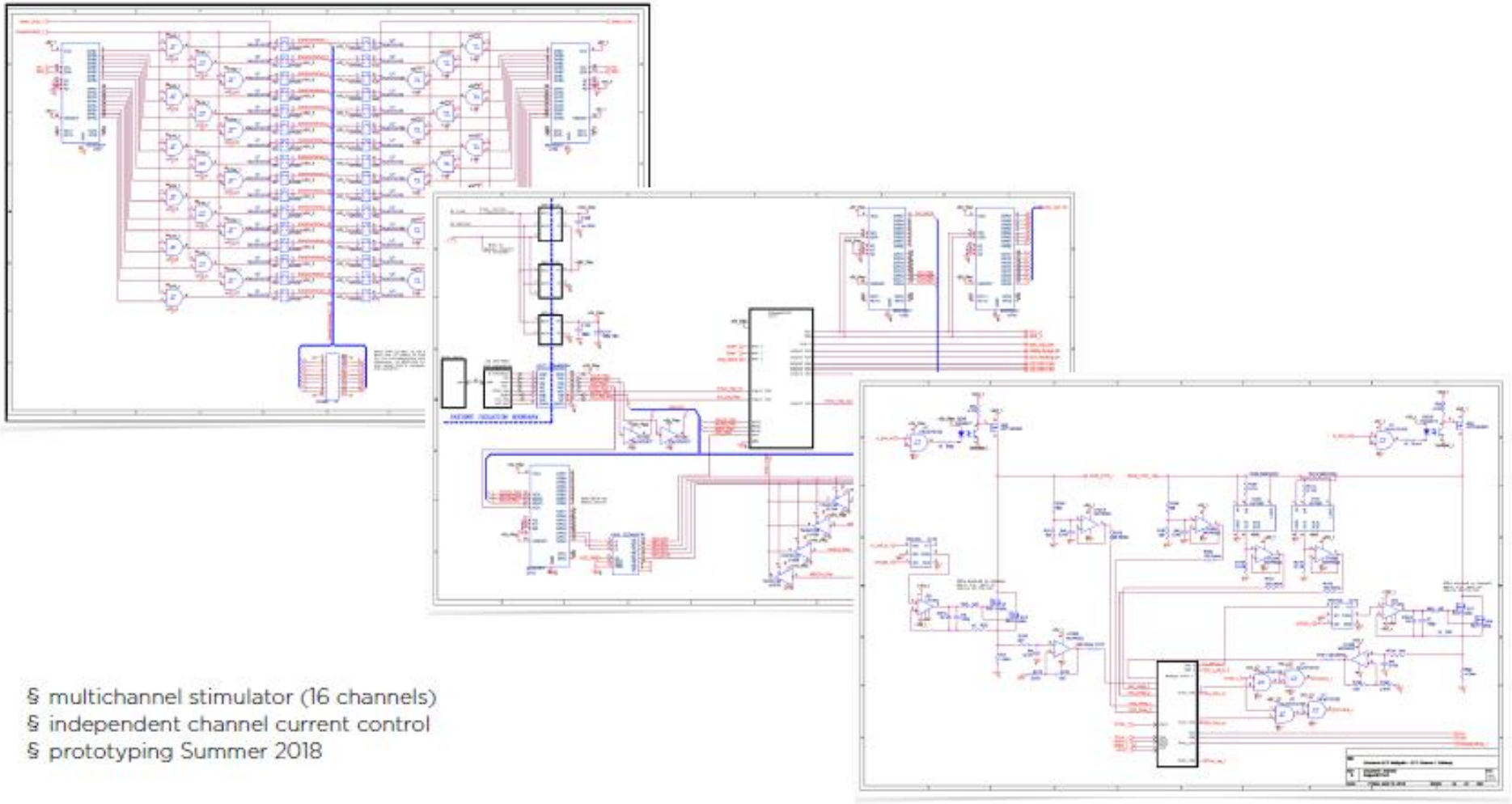
n = 10 completers

| | Phase I: Baseline | Phase II: iLAST | Phase III: RUL ECT |
|---|---|---|---|
| Screening<br><br>Informed consent | Clinical & neurocognitive assessment with *video recording<br><br>Neuroimaging (MRI, DTI, *EEG-fMRI resting and task, *TMS-fMRI, *MEG)<br><br>*Cortical excitability/ plasticity assessment | Session 1-7: HD-RUL × 1 , iECT-MC × 2, iECT-VX × 2, iECT-PFC × 2 (random order)<br><br>Peri treatment assessment<br>-Acute neurocog battery<br>-Acute clinical assessment<br>-*Video recording of neurocog/clinical assessment<br>-resting EEG, *TMS-EP | Standard course of RUL ECT<br>+ *full montage ictal EEG<br><br>Pre & Post acute course clinical/neurocog/ *neuroimaging/ *plasticity assessment<br><br>Relapse prevention/ maintainence |

5 electrode adaptor

# Next generation seizure therapy



- multichannel stimulator (16 channels)
- independent channel current control
- prototyping Summer 2018

Pritchard & Deng, 2018

# Conclusions

- New therapies for treatment resistant depression:
  - Non-convulsive:  RDOC-based, fMRI-guided TMS
    - Individualized, based on engaging cortical circuitry involved in depression
  - Convulsive: MST and iLAST
    - Individualized, lower-intensity stimulation that induces therapeutic seizures but with less cognitive side effects
- Using the latest neuroscience to guide treatment development

# Acknowledgments

**ETPB Principal Investigators:**
Holly Lisanby, M.D.
Carlos Zarate, M.D.

**NIMH Associate Investigators and Staff Scientists:**

Allison Nugent, Ph.D
Lawrence Park, M.D.
Wally Duncan, M.D.
Elizabeth Ballard, Ph.D.
Thomas Radman, Ph.D.
Zhi-De Deng, Ph.D.

**Columbia University Collaborators:**

Yaakov Stern
Paul Sajda
Dave Jangraw
Chris Habeck
Jason Steffener
Brian Rakitin
James Moeller
Teresa Nguyen
Peter Bulow

**Duke University Collaborators:**

Tim Strauman
Andrada Neacsiu
Simon Davis
Roberto Cabeza
Greg Appelbaum
Lysianne Beynel
David Murphy
Angel Peterchev
Lis Bernhardt

**Funding**

NIMH
NIA
DARPA

For more information email moodresearch@mail.nih.gov or call 1-877-MIND-NIH (1-877-646-3644)