



Stanford | MEDICINE

BRAIN STIMULATION LABORATORY

Stanford Accelerated Intelligent Neuromodulation Therapy

Nolan Williams MD

Assistant Professor

Department of Psychiatry and Behavioral Sciences

Stanford University

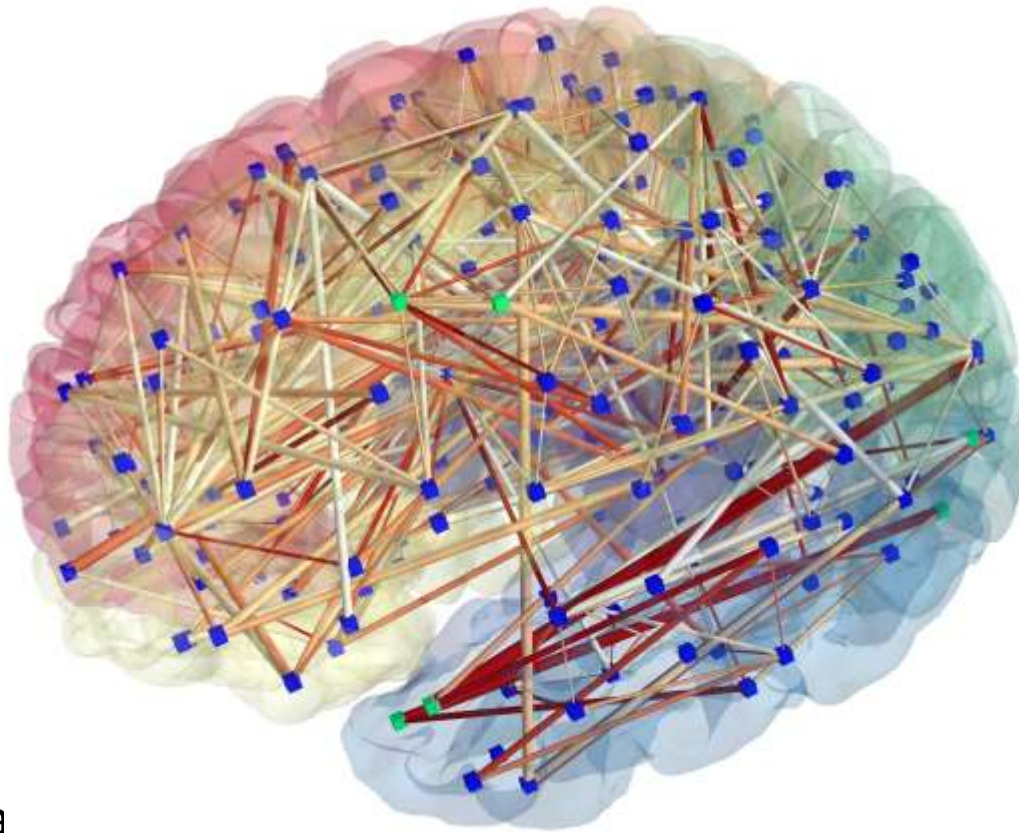
Goals of Talk

- To provide a background for neuromodulation treatments for depression.
- To discuss recent findings specifically in theta burst TMS.
- To demonstrate new rapid-acting brain stimulation method.

All Neuropsychiatric Diseases Are Disorders of Distributed Neural Networks

“Neurological Conditions”

- Parkinson’s disease
- Tourette syndrome
- Alzheimer’s disease
- Generalized Dystonia



“Psychiatric Conditions”

- Major Depression
- Bipolar Disorder
- Obsessive-Compulsive Disorder
- Post Traumatic Stress Disorder

Major depressive disorder (MDD)



Prevalent

1 in 5 American adults (~63M)
experience clinical depression at
some point in life

7.1% of American adults (~17M)
will have clinical depression this
year



Disabling

Leading cause of disability
worldwide

Economic burden of depression
in America is over \$210B
annually



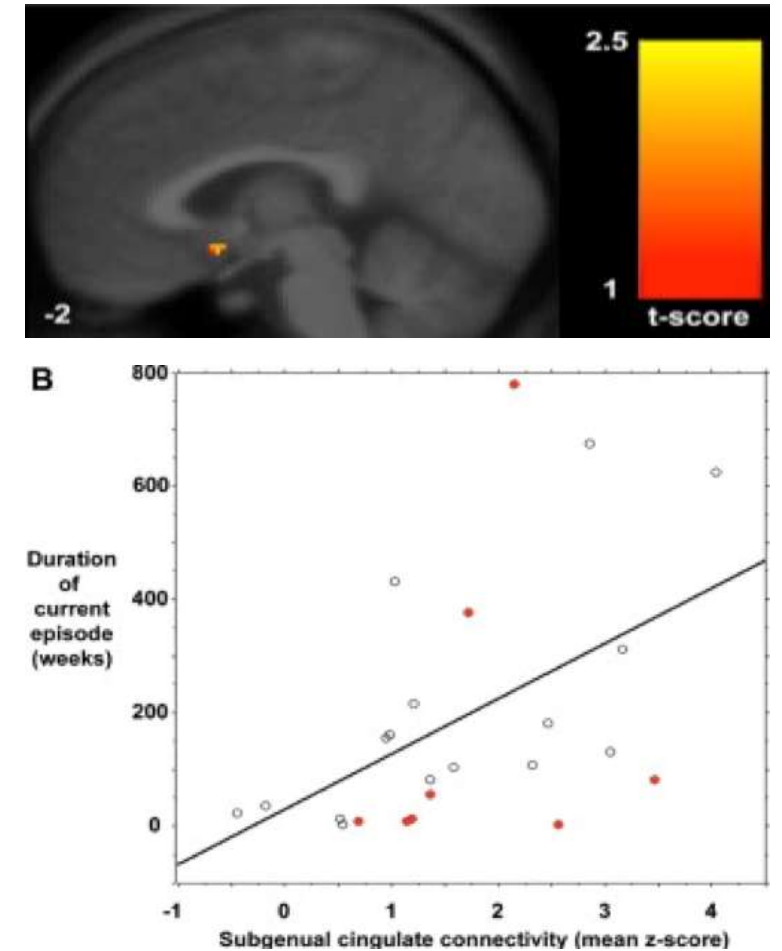
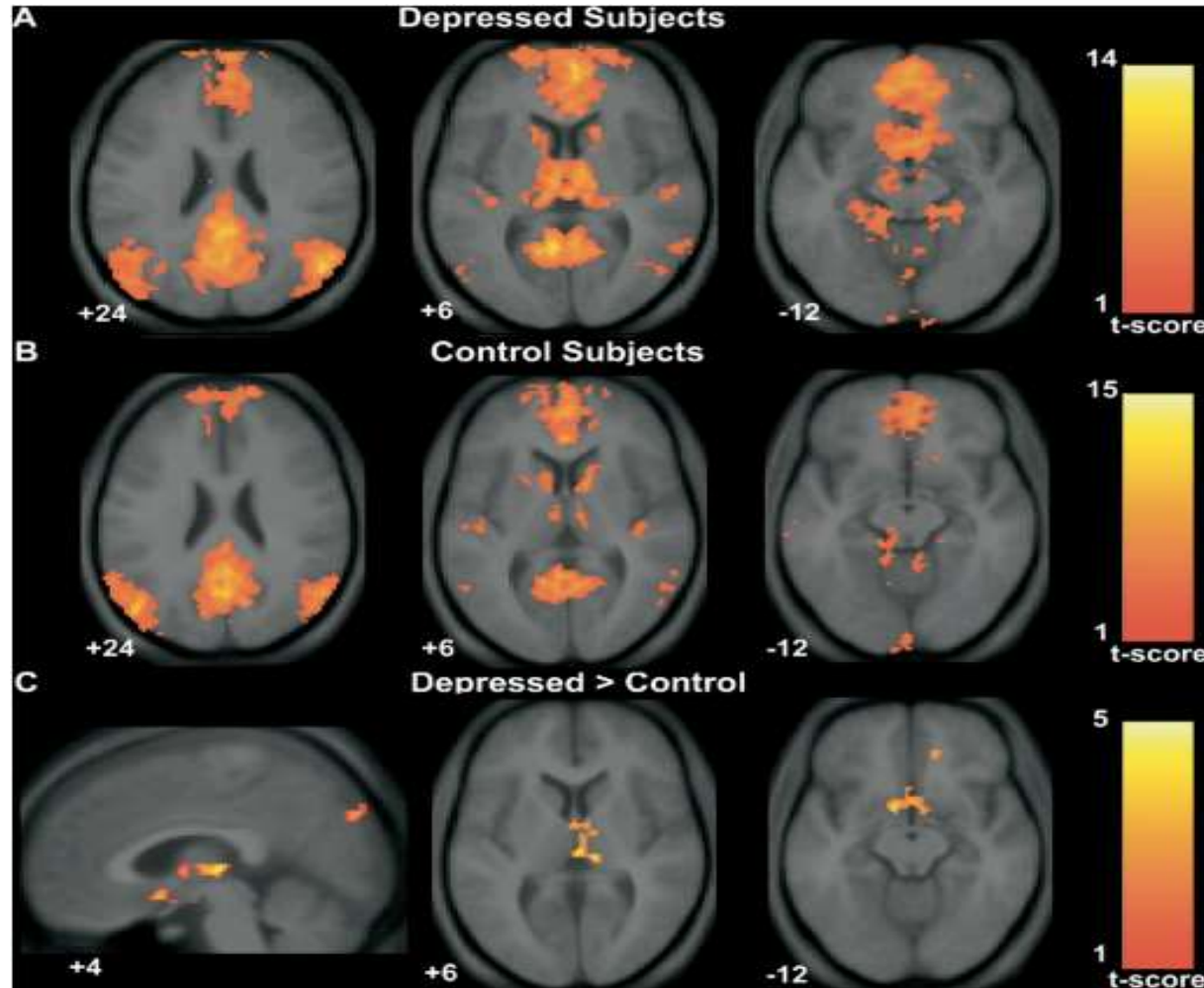
Treatment resistant (TRD)

Treatments are slow (4-14 weeks to response),
with limited effectiveness

20-30% of MDD patients do not respond to
anything (this is TRD)

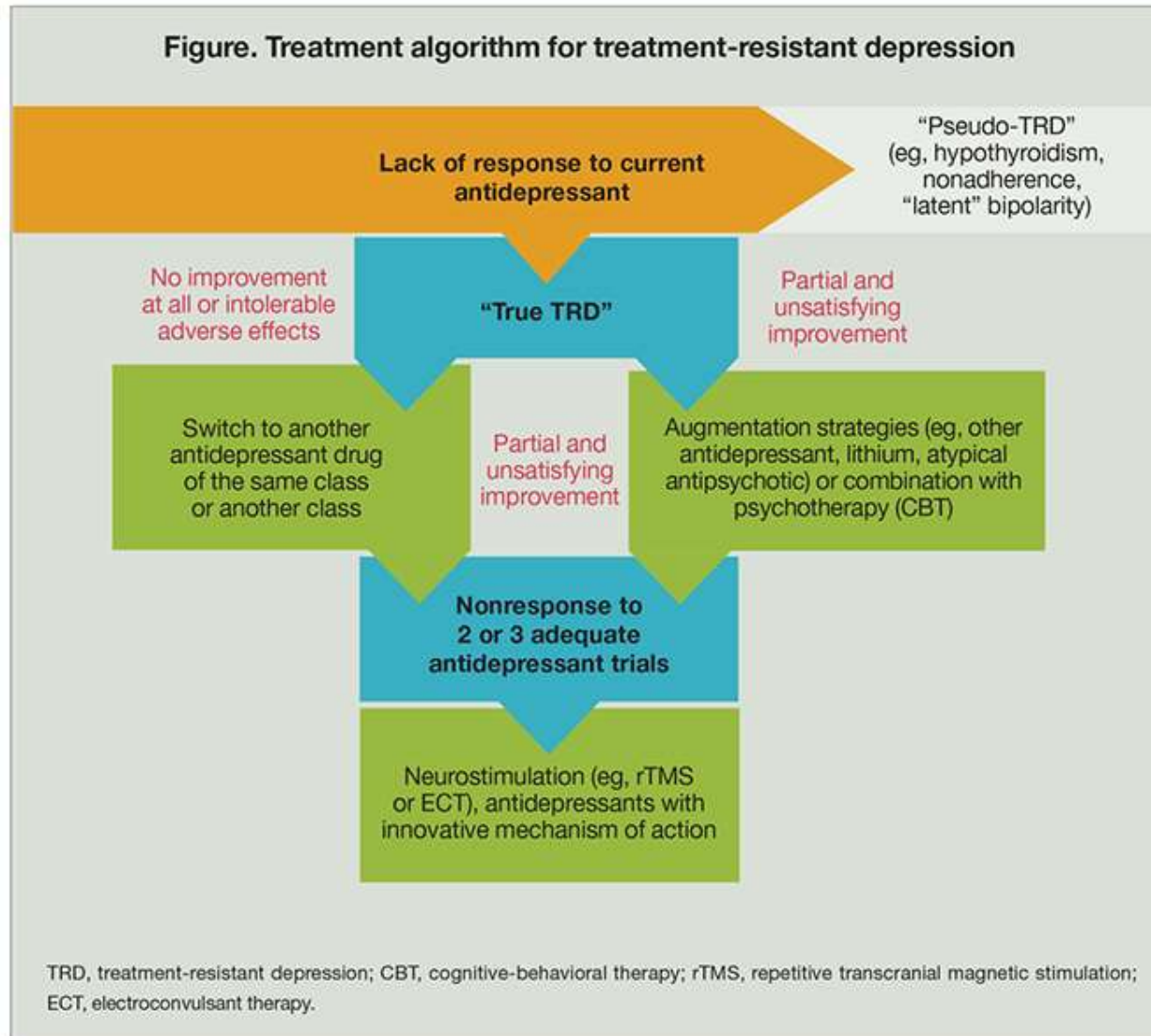
Antidepressants do not affect suicidality

Depression is a Disorder of Large-Scale Functional Networks

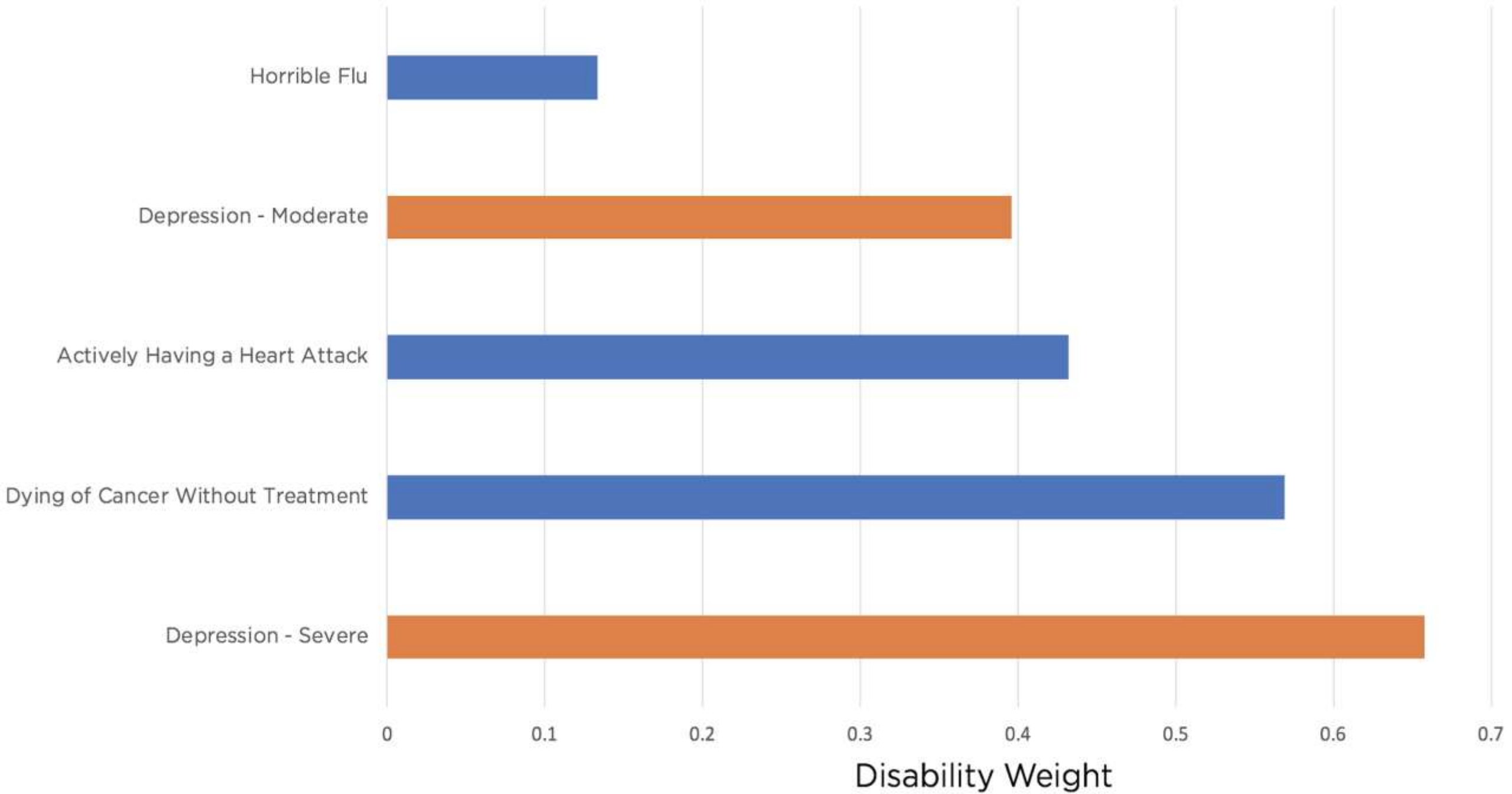


Greicius, Biol Psych, 2007

Current State of the Art for TRD



Melancholy by Albert György






- **Medications are insufficient for 5.5M**
- **\$38B additional all-cause cost of care**



- **550,000 hospitalized**
- **Average stay 7.4 days**
- **\$11B cost to system**
- **Suicidality peaks 3x at discharge**

Psychiatric beds 3x overloaded, \$2.1B lost per year





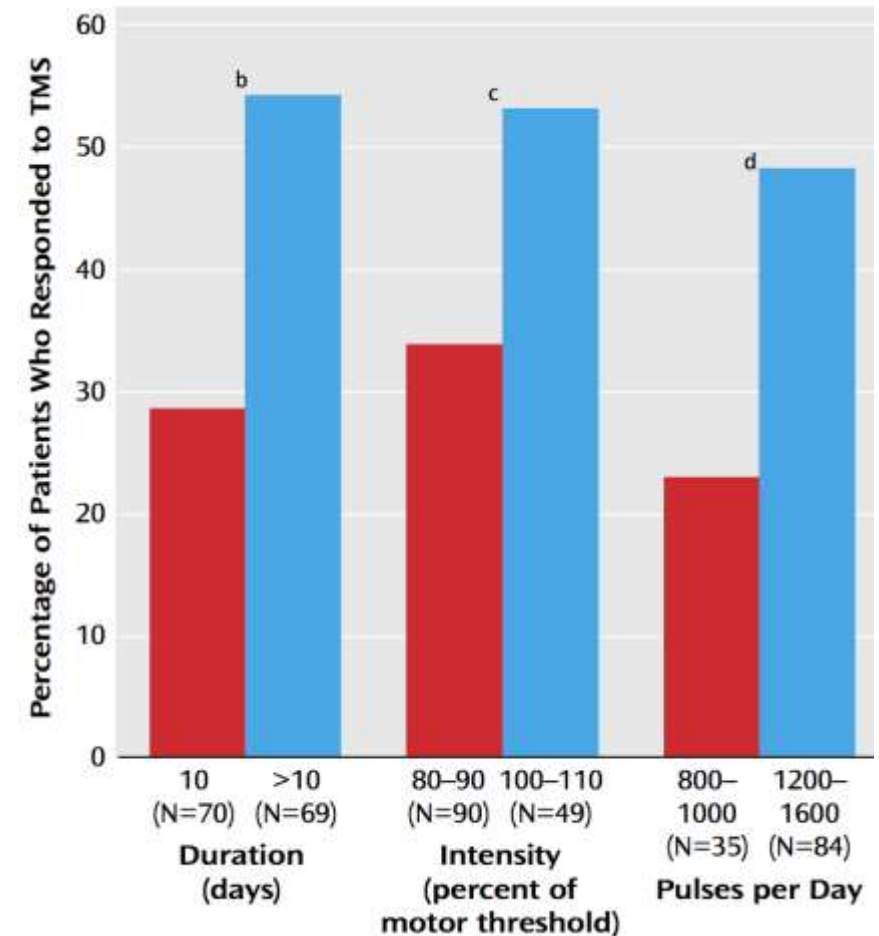
What if mental
health treatments
were designed, not
discovered?

Conventional Repetitive Transcranial Magnetic Stimulation

First Generation Stimulation Parameters



- The first reported patient received excitatory left dorsolateral prefrontal cortex in 1995 (L DLPFC) stimulation (George 1995).
- L DLPFC target selected based off of converging clinical and neuroimaging evidence (George 1994).
- Parameters derived from motor physiology findings (Pascual-Leon, 1994).
- The parameters evolved over time with longer duration, higher intensities, and more pulses per day producing greater efficacy.



Original FDA Approved rTMS Parameters

- Frequency: 10Hz
- Pulse Potency: 1X
- Train Duration: 4 seconds
- Inter-train Interval: 26 seconds
- Pulse Dose/session: 3000 pulses/session
- %MT: 120% rMT
- Sessions/day: 1
- Sessions/week: 5
- Sessions/course: 30
- Pulses/course: 90,000 pulses
- Target: L DLPFC
- Targeting: skull-based measurements

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Mon	Mon	Mon	Mon	Mon	Mon
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Tues	Tues	Tues	Tues	Tues	Tues
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Wed	Wed	Wed	Wed	Wed	Wed
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Thurs	Thurs	Thurs	Thurs	Thurs	Thurs
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Fri	Fri	Fri	Fri	Fri	Fri

First Generation Stimulation Parameters

- In open label settings, ~30% remit and ~50% respond after this course.
- 62% of patient maintain response/remission at 6 mo and that increases to 84% if mTMS added in.
- Recent data suggests more pulses may increase efficacy (Yip 2017).

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Mon	Mon	Mon	Mon	Mon	Mon
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Tues	Tues	Tues	Tues	Tues	Tues
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Wed	Wed	Wed	Wed	Wed	Wed
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Thurs	Thurs	Thurs	Thurs	Thurs	Thurs
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Fri	Fri	Fri	Fri	Fri	Fri

iTBS is Biologically Active for TRD

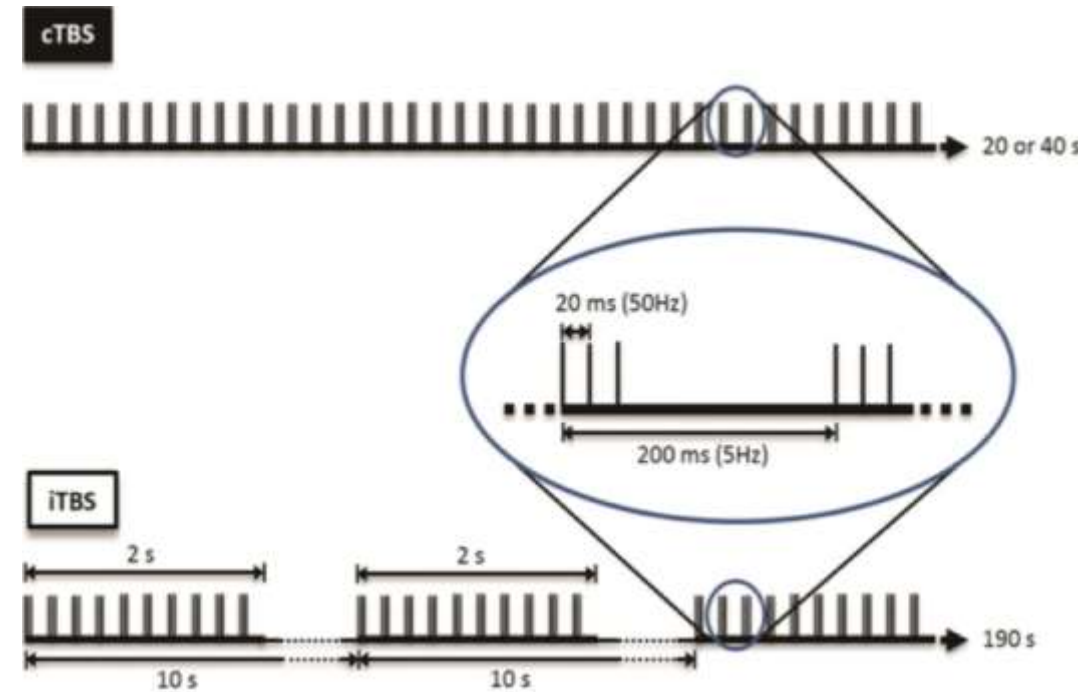
Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Mon	Mon	Mon	Mon	Mon	Mon
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Tues	Tues	Tues	Tues	Tues	Tues
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Wed	Wed	Wed	Wed	Wed	Wed
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Thurs	Thurs	Thurs	Thurs	Thurs	Thurs
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Fri	Fri	Fri	Fri	Fri	Fri

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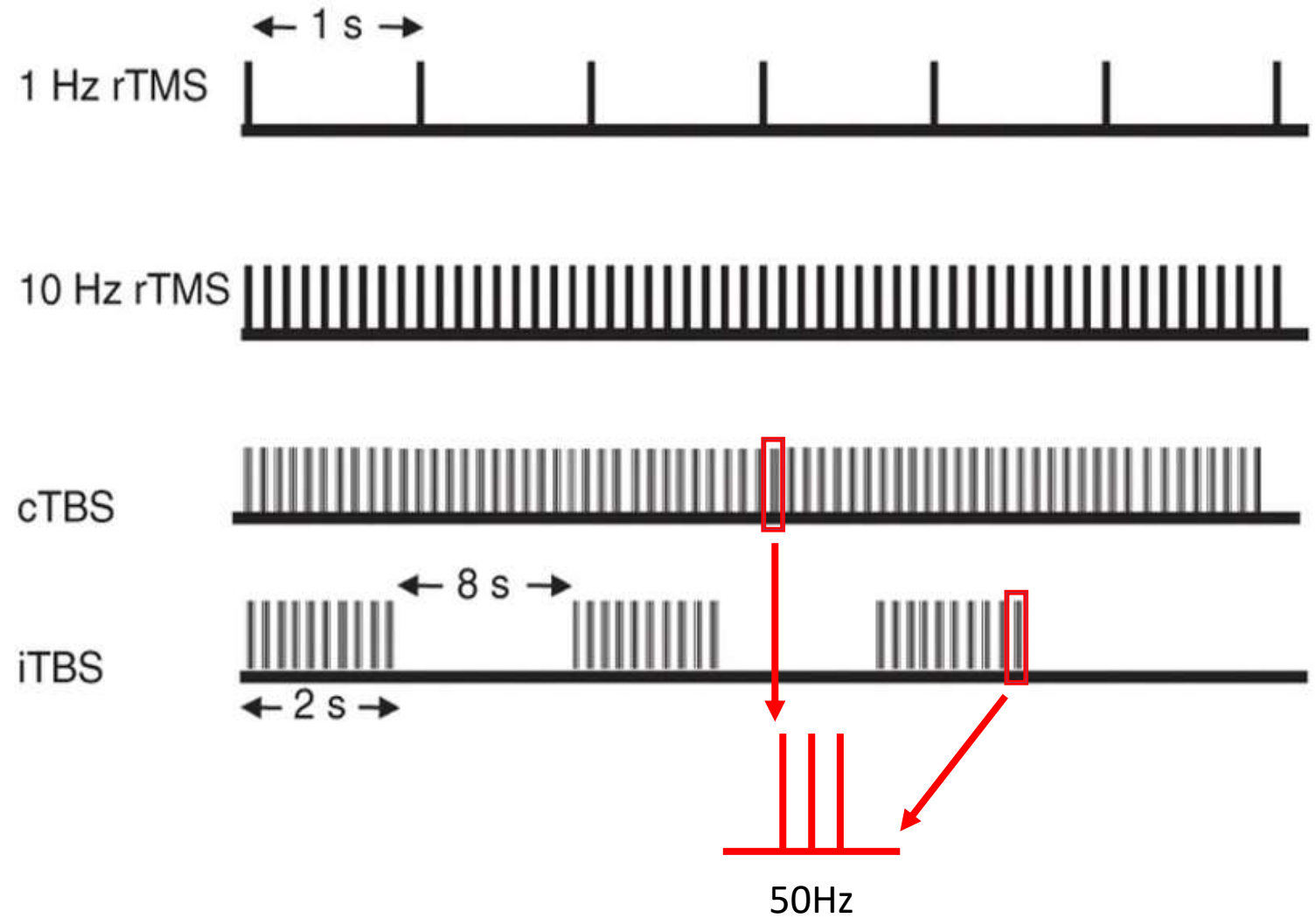
Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Mon	Mon	Mon	Mon	Mon	Mon
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Tues	Tues	Tues	Tues	Tues	Tues
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Wed	Wed	Wed	Wed	Wed	Wed
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Thurs	Thurs	Thurs	Thurs	Thurs	Thurs
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Fri	Fri	Fri	Fri	Fri	Fri

Second Generation Stimulation Parameters

- Human motor physiology studies have demonstrated that Theta-Burst Stimulation (TBS) when applied intermittently (iTBS), produces excitation in cortex (Huang 2005).
- 600 pulses of iTBS can be applied in 3 min and this application is equivalent to 3000 pulses of 10Hz (37 min) as far as motor cortical excitability.
- Allows for much more efficient application of pulses /session.

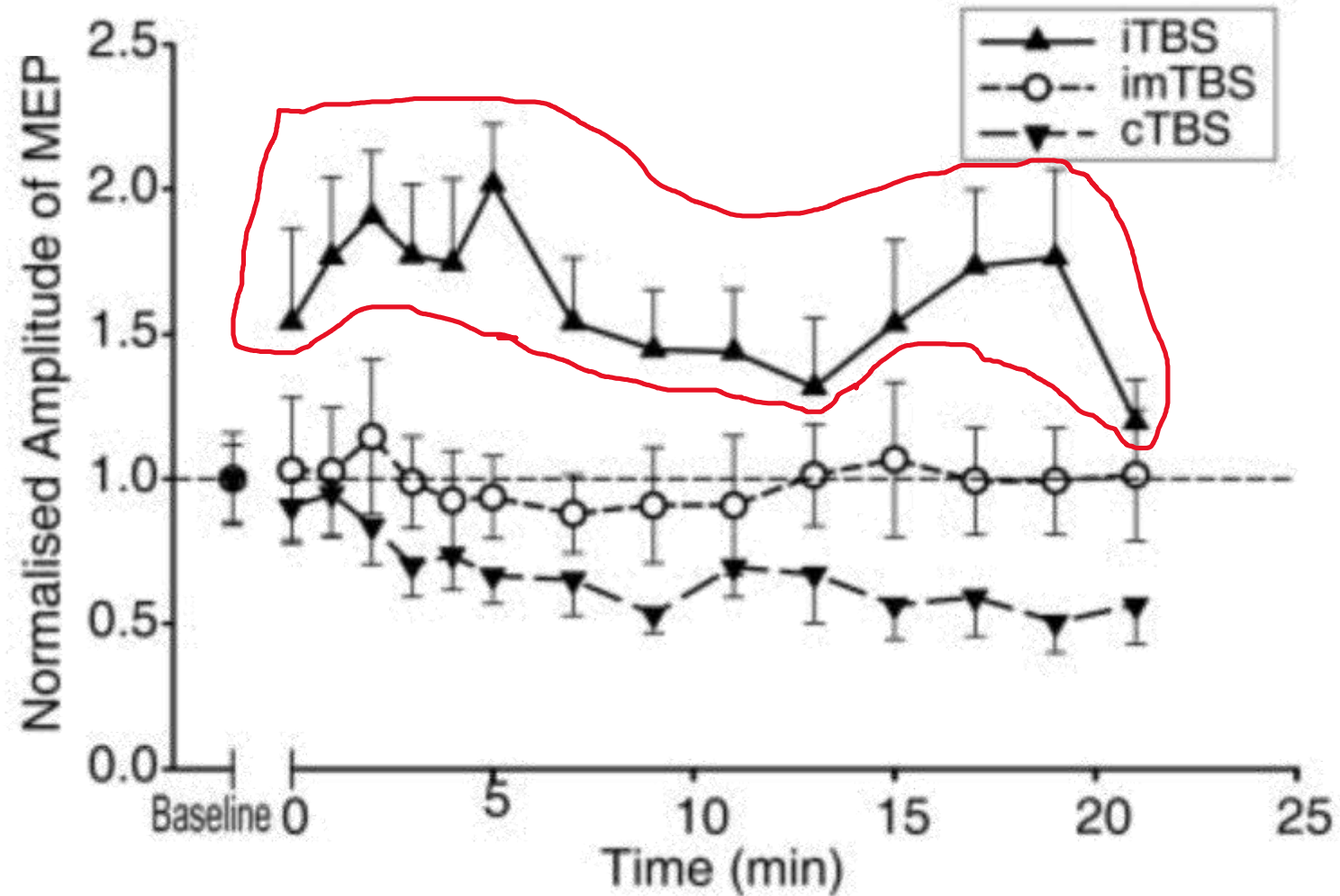


Comparing TBS to standard clinical rTMS



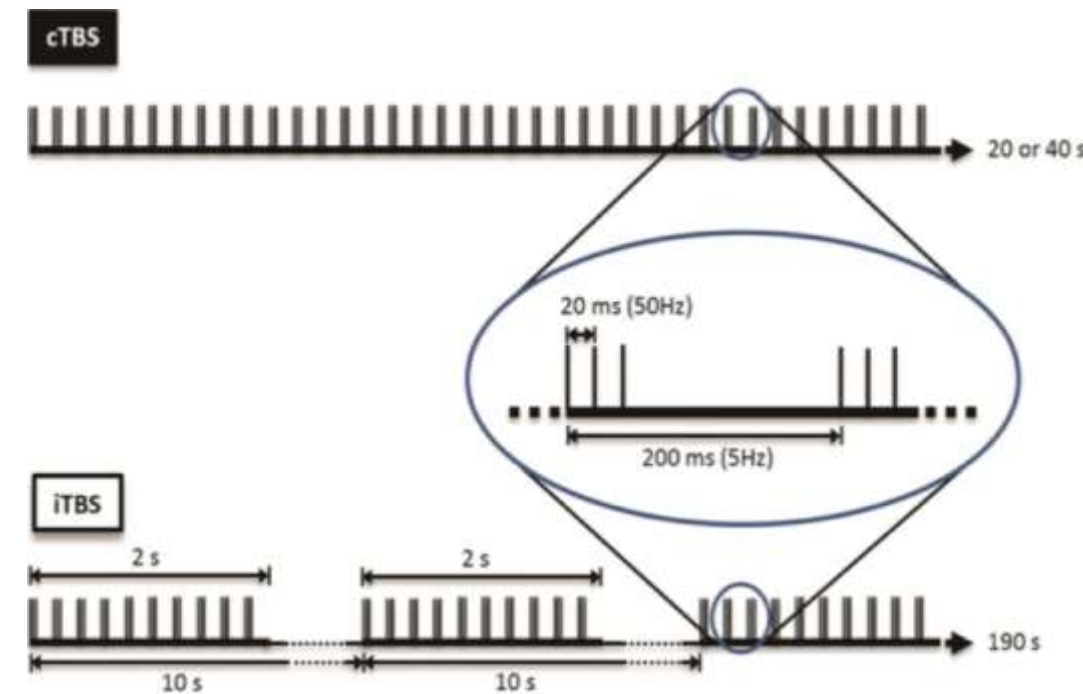
TBS via TMS in humans potentiates cortex

Huang Y-Z, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. 2005 Jan 20;45(2):201–206. PMID: 15664172



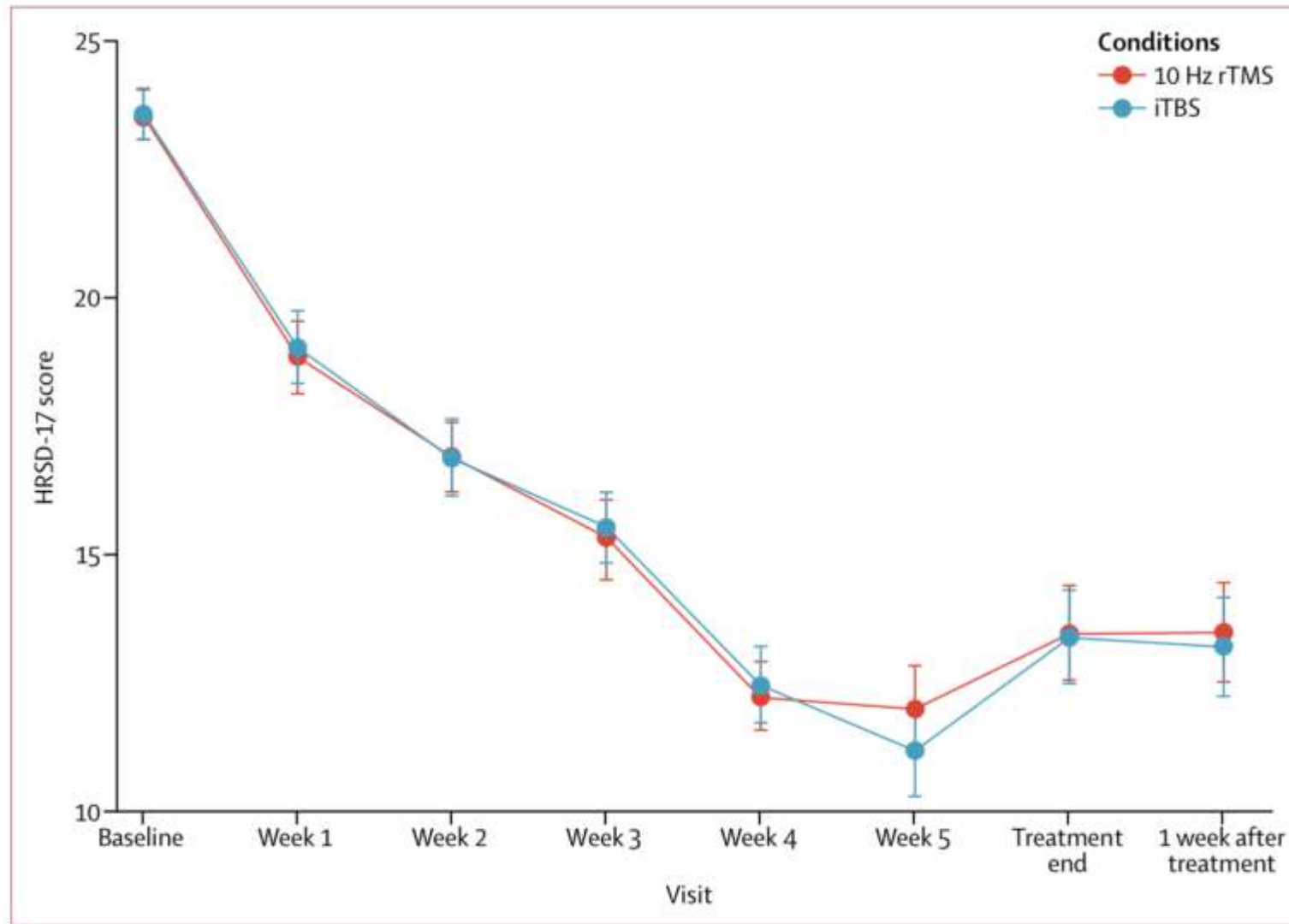
Second Generation Stimulation Parameters

- A recently completed non-inferiority trial demonstrated that 600 pulses of iTBS (3 min protocol) is non-inferior to 3,000 pulses of 10hz rTMS (37 min protocol) in ~400 subjects (Blumberger 2018).
- 1,800 pulses of iTBS over L DLPFC has been demonstrated to be effective in treating moderate TRD (Li 2012).
- iTBS when applied at least 50 min apart produces robust LTP induction (Kramar 2012, Lynch 2013).



iTBS of L-DLFPC is an efficient treatment for depression

Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, Knyahnytska Y, Kennedy SH, Lam RW, Daskalakis ZJ, Downar J. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet*. 2018 Apr 28;391(10131):1683–1692. PMID: 29726344



FDA-Approved Single Daily iTBS Parameters

- Frequency: 5Hz/50Hz (iTBS)
- Pulse Potency: 5X
- Train Duration: 2 seconds
- Inter-train Interval: 8 seconds
- Pulse Dose/session: 600 pulses/session
- %MT: 120% rMT
- Sessions/day: 1
- Sessions/week: 5
- Sessions/course: 30
- Pulses/course: 18,000 pulses
- Target: L DLPFC
- Targeting: Average MNI Coordinate

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Mon	Mon	Mon	Mon	Mon	Mon
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Tues	Tues	Tues	Tues	Tues	Tues
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Wed	Wed	Wed	Wed	Wed	Wed
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Thurs	Thurs	Thurs	Thurs	Thurs	Thurs
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Fri	Fri	Fri	Fri	Fri	Fri

iTBS is Biologically Active for TRD

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Mon	Mon	Mon	Mon	Mon	Mon
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Tues	Tues	Tues	Tues	Tues	Tues
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Wed	Wed	Wed	Wed	Wed	Wed
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Thurs	Thurs	Thurs	Thurs	Thurs	Thurs
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Fri	Fri	Fri	Fri	Fri	Fri

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Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Mon	Mon	Mon	Mon	Mon	Mon
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Tues	Tues	Tues	Tues	Tues	Tues
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Wed	Wed	Wed	Wed	Wed	Wed
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Thurs	Thurs	Thurs	Thurs	Thurs	Thurs
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Fri	Fri	Fri	Fri	Fri	Fri

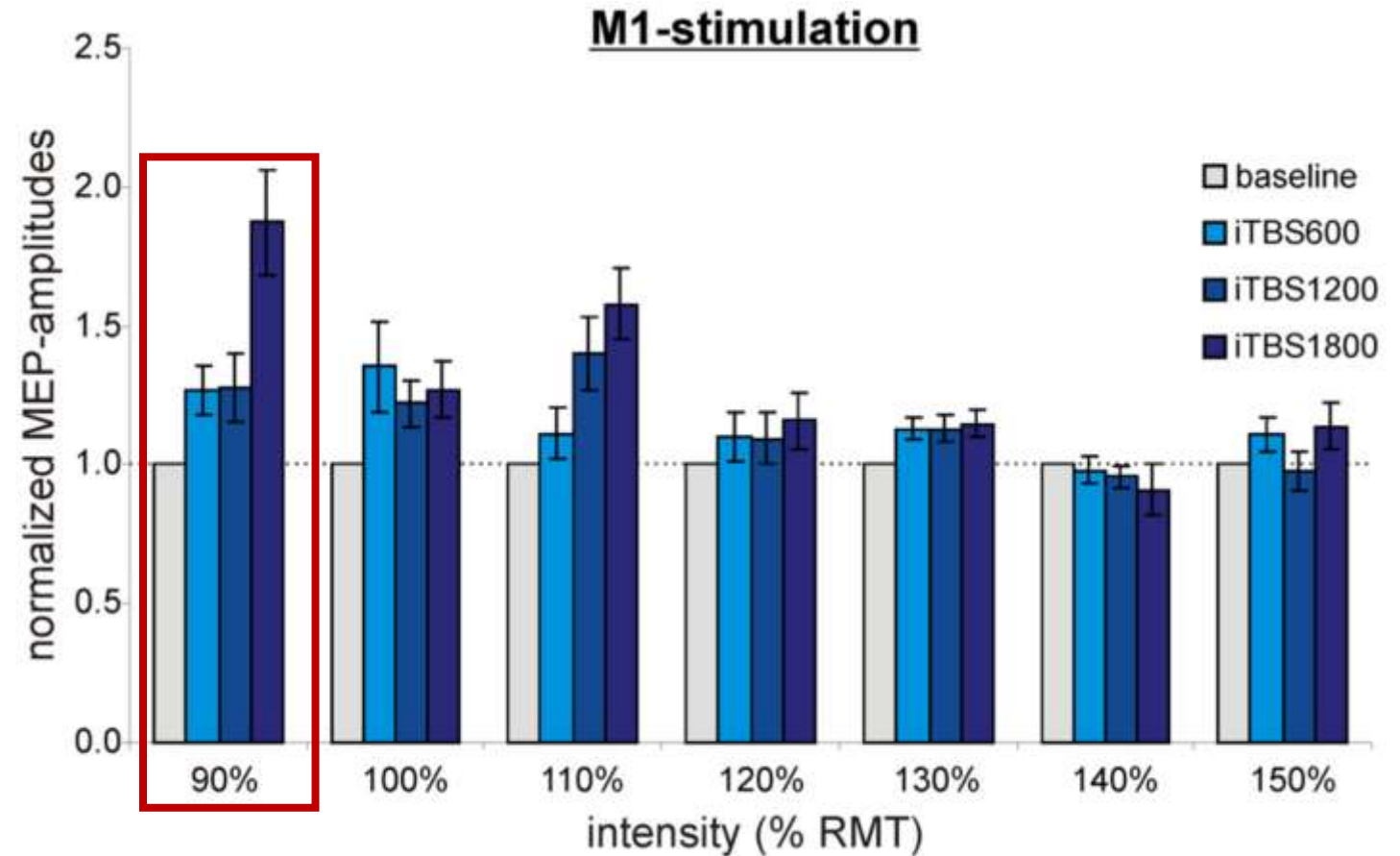
SAINT

iTBS, 90% MT, 1800 pulses, 60min spacing, high-dose, and targeted

~90% MT may be
the optimal
stimulation
intensity

Nettekoven C, Volz LJ, Kutscha M, Pool E-M, Rehme AK, Eickhoff SB, Fink GR, Grefkes C. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. Journal of Neuroscience. 2014 May 14;34(20):6849–6859. PMCID: PMC4019799

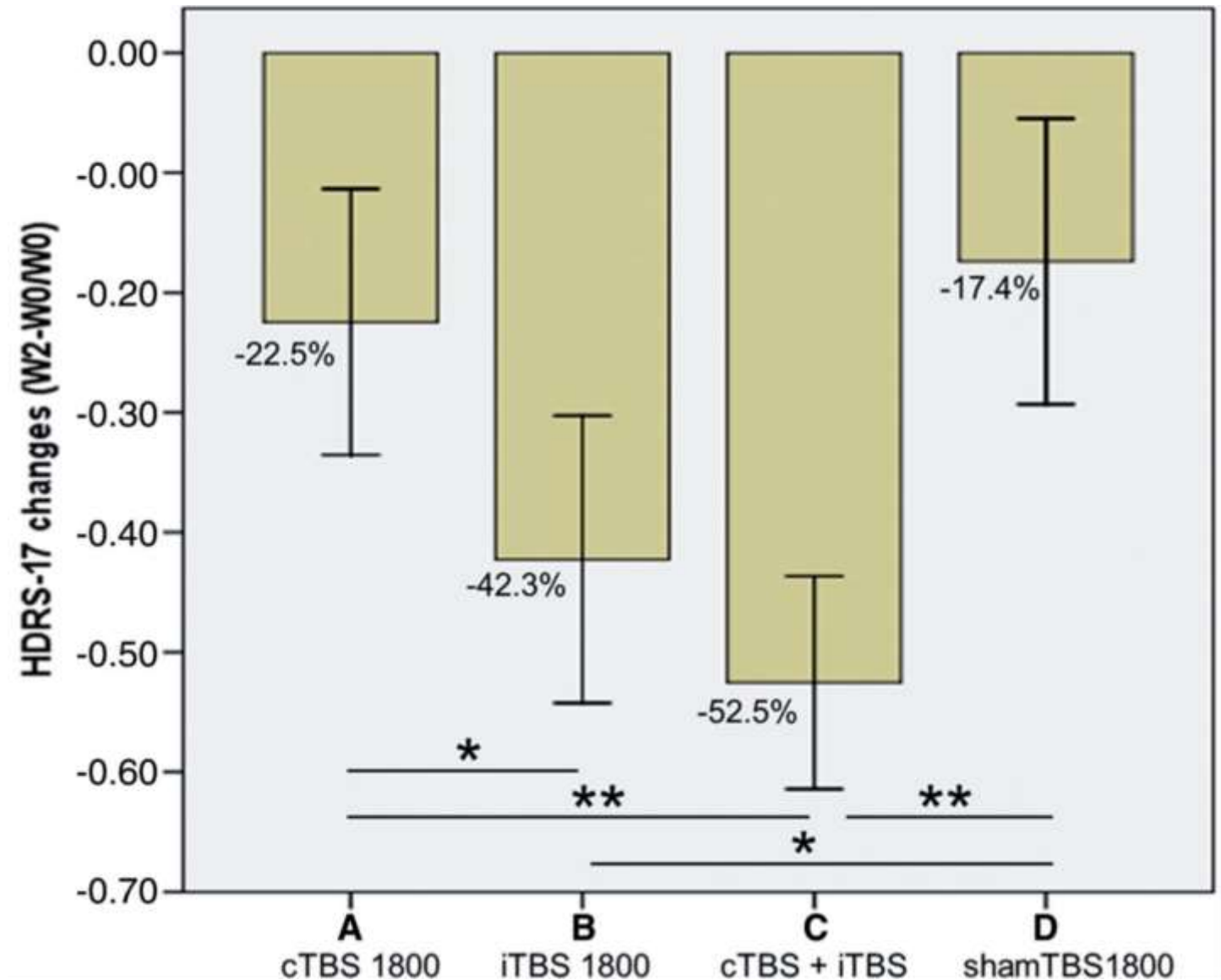
90% MT Stimulation



1800 Pulses per session found to be effective for depression

Li C-T, Chen M-H, Juan C-H, Huang H-H, Chen L-F, Hsieh J-C, Tu P-C, Bai Y-M, Tsai S-J, Lee Y-C, Su T-P. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. *Brain*. 2014 Jul;137(Pt 7):2088–2098. PMID: 24817188

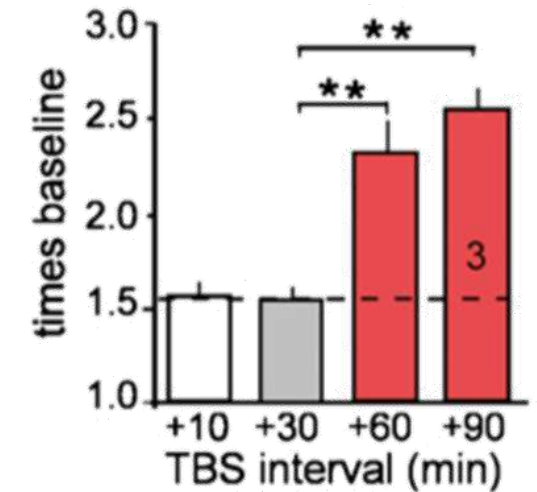
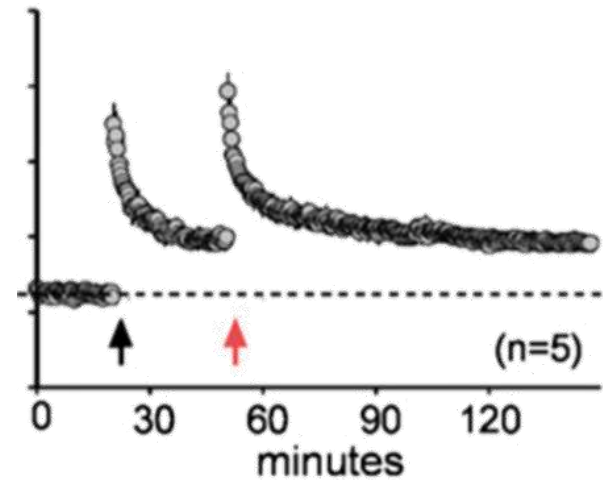
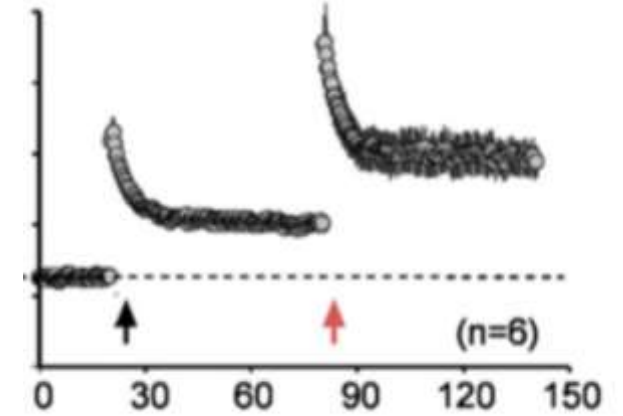
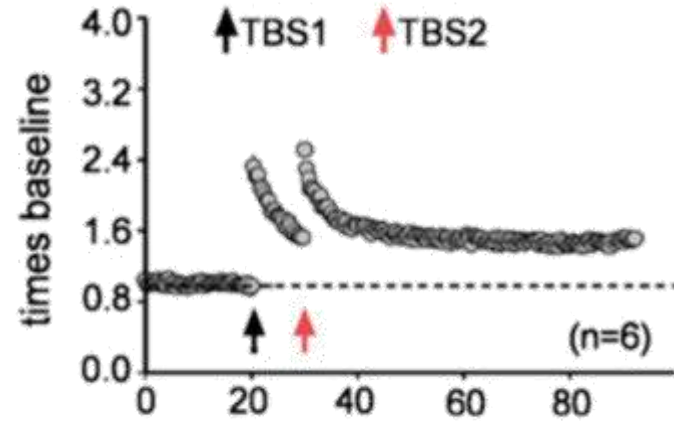
1800 Pulses per session



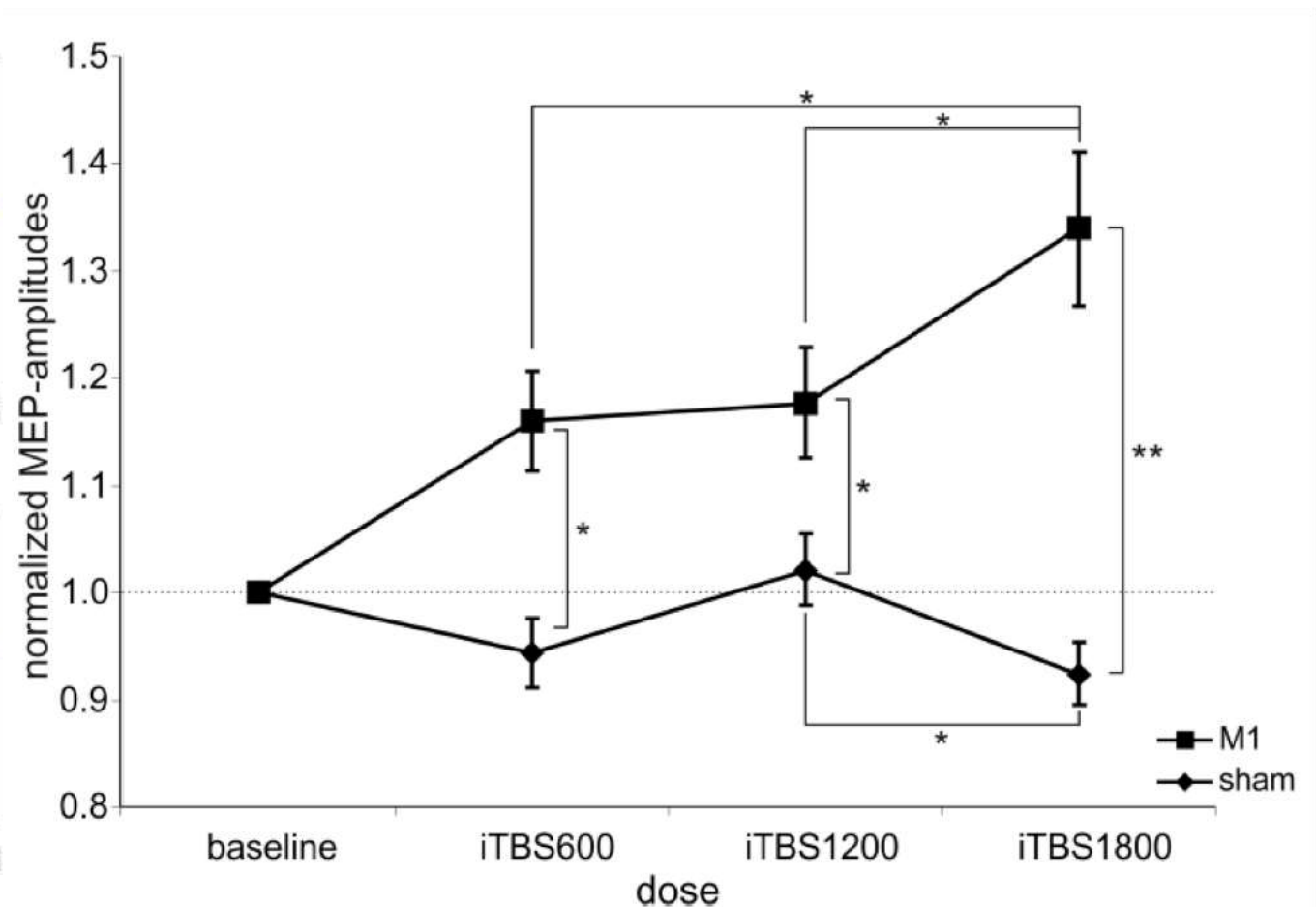
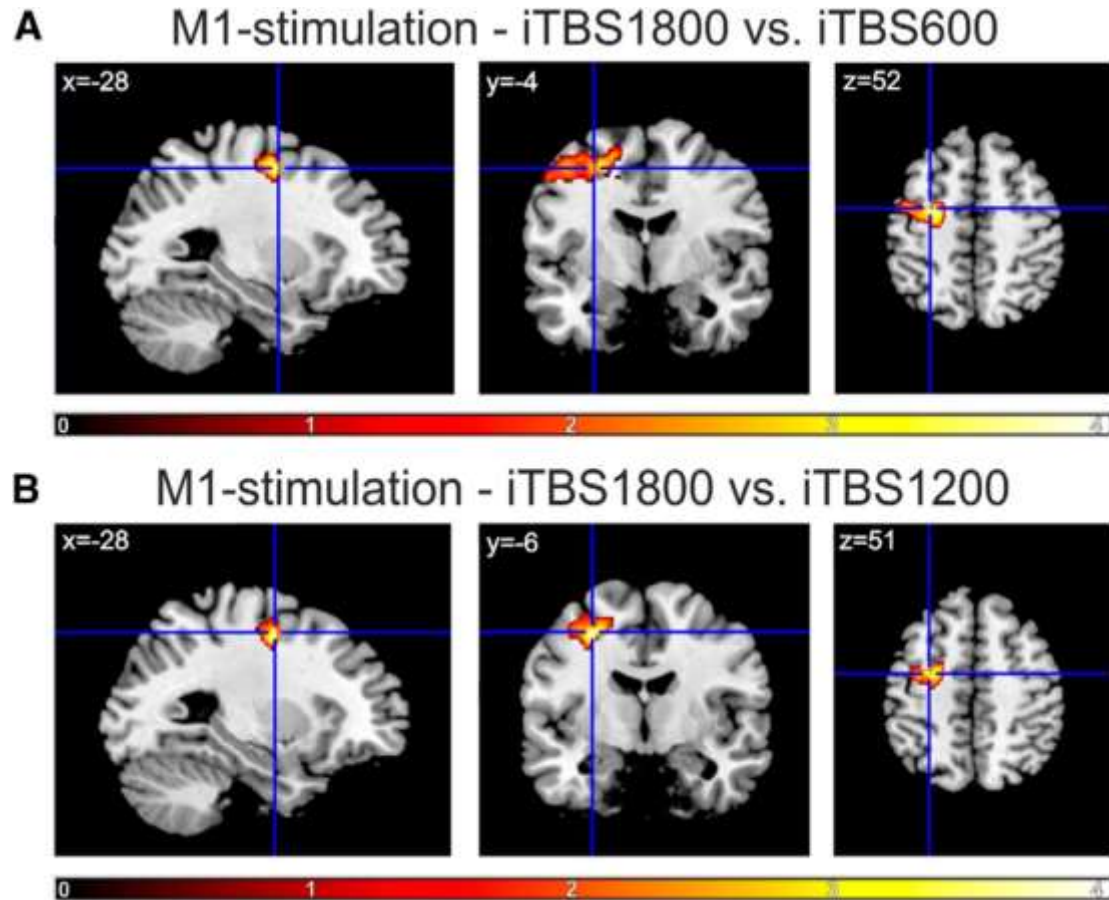
60min spacing

TBS spaced by
60min produces
long last
potentiation in
rodents

Kramár EA, Babayan AH, Gavin CF, Cox CD, Jafari M, Gall CM, Rumbaugh G, Lynch G. Synaptic evidence for the efficacy of spaced learning. *Proceedings of the National Academy of Sciences*. 2012 Mar 27;109(13):5121–5126. PMCID: PMC3323981



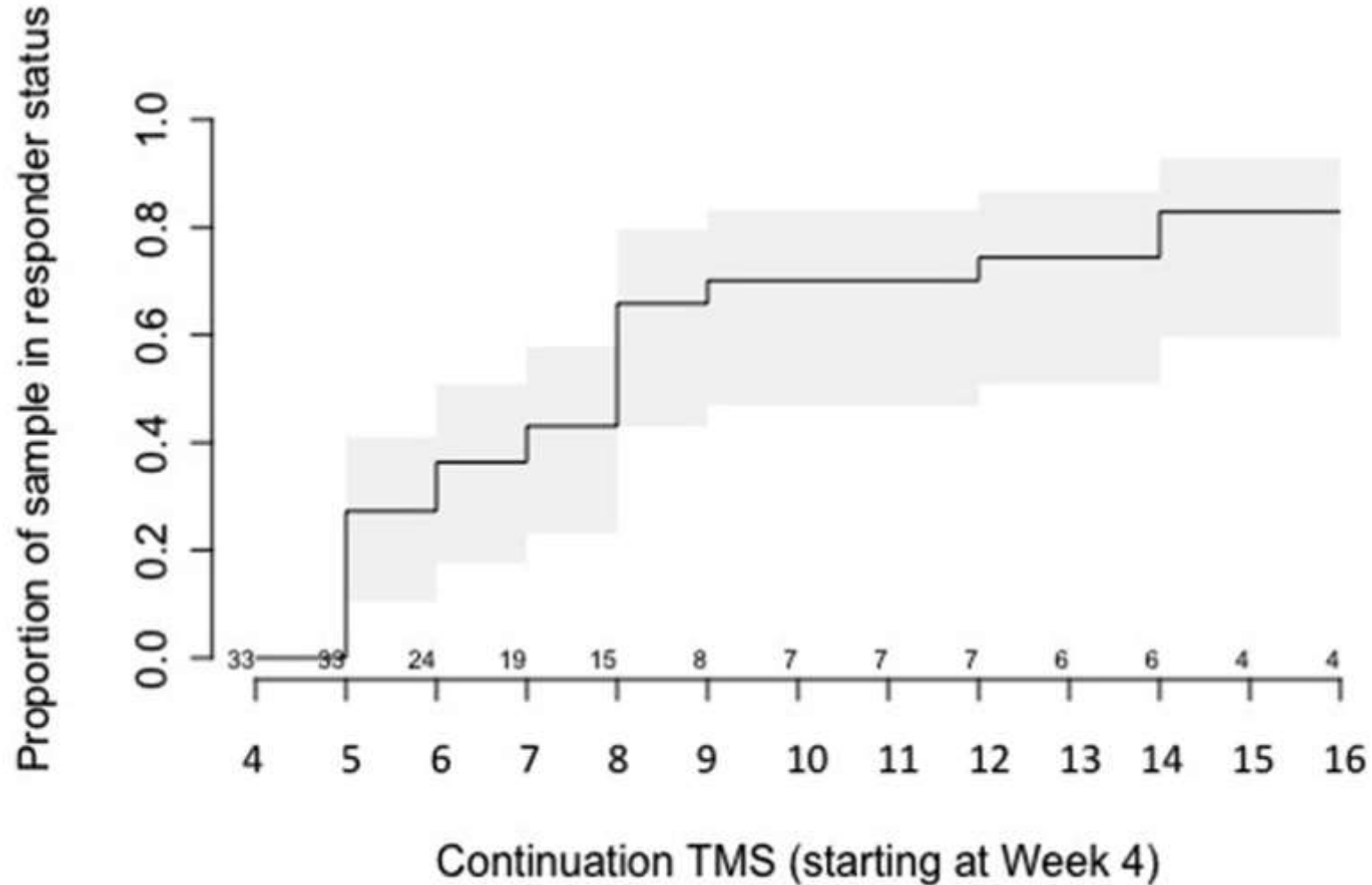
Inter-session Interval Based off of Motor Physiology Experiments



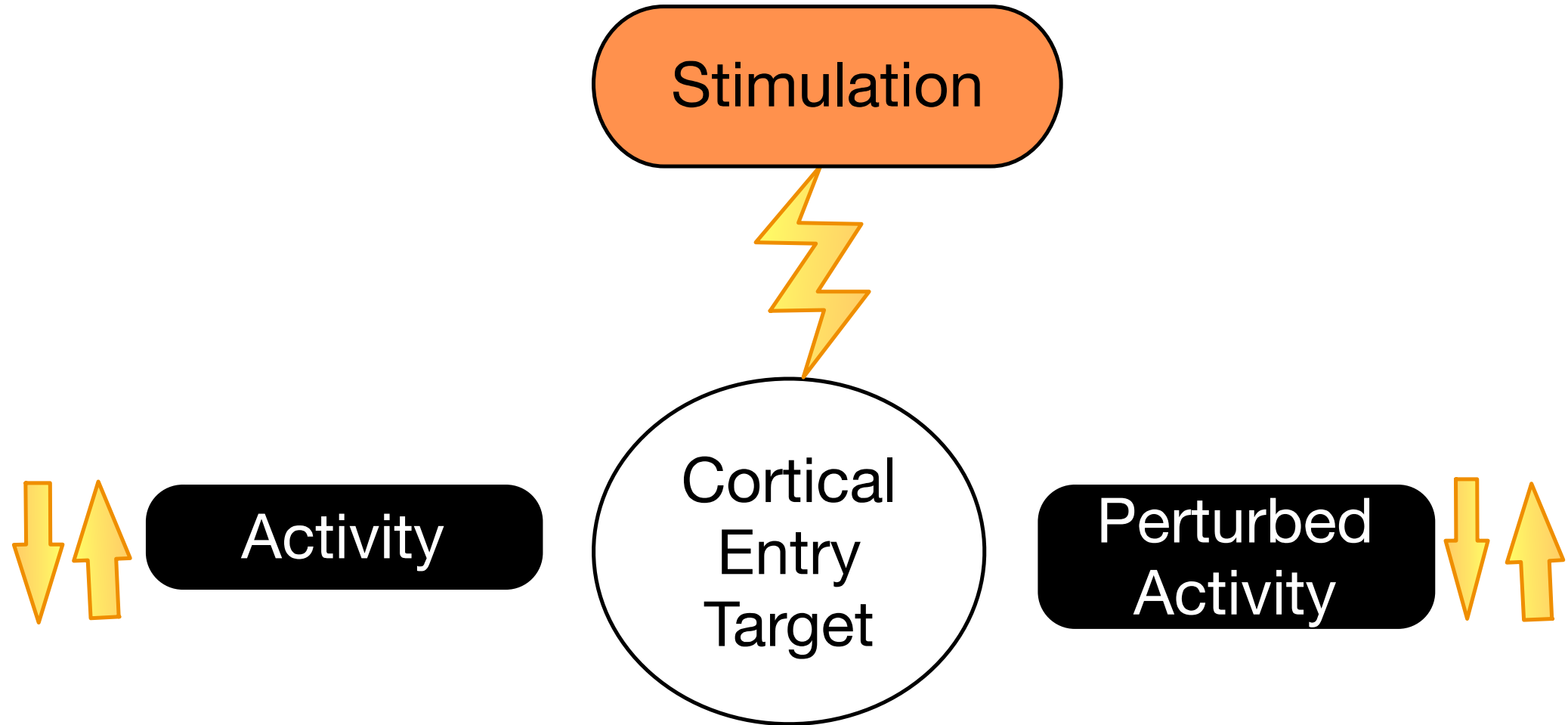
High Dose

More TMS
sessions → more
responders

Yip AG, George MS, Tendler A, Roth Y, Zangen A, Carpenter LL. 61% of unmedicated treatment resistant depression patients who did not respond to acute TMS treatment responded after four weeks of twice weekly deep TMS in the Brainsway pivotal trial. Brain Stimul. 2017 Aug;10(4):847–849. PMID: 28330592

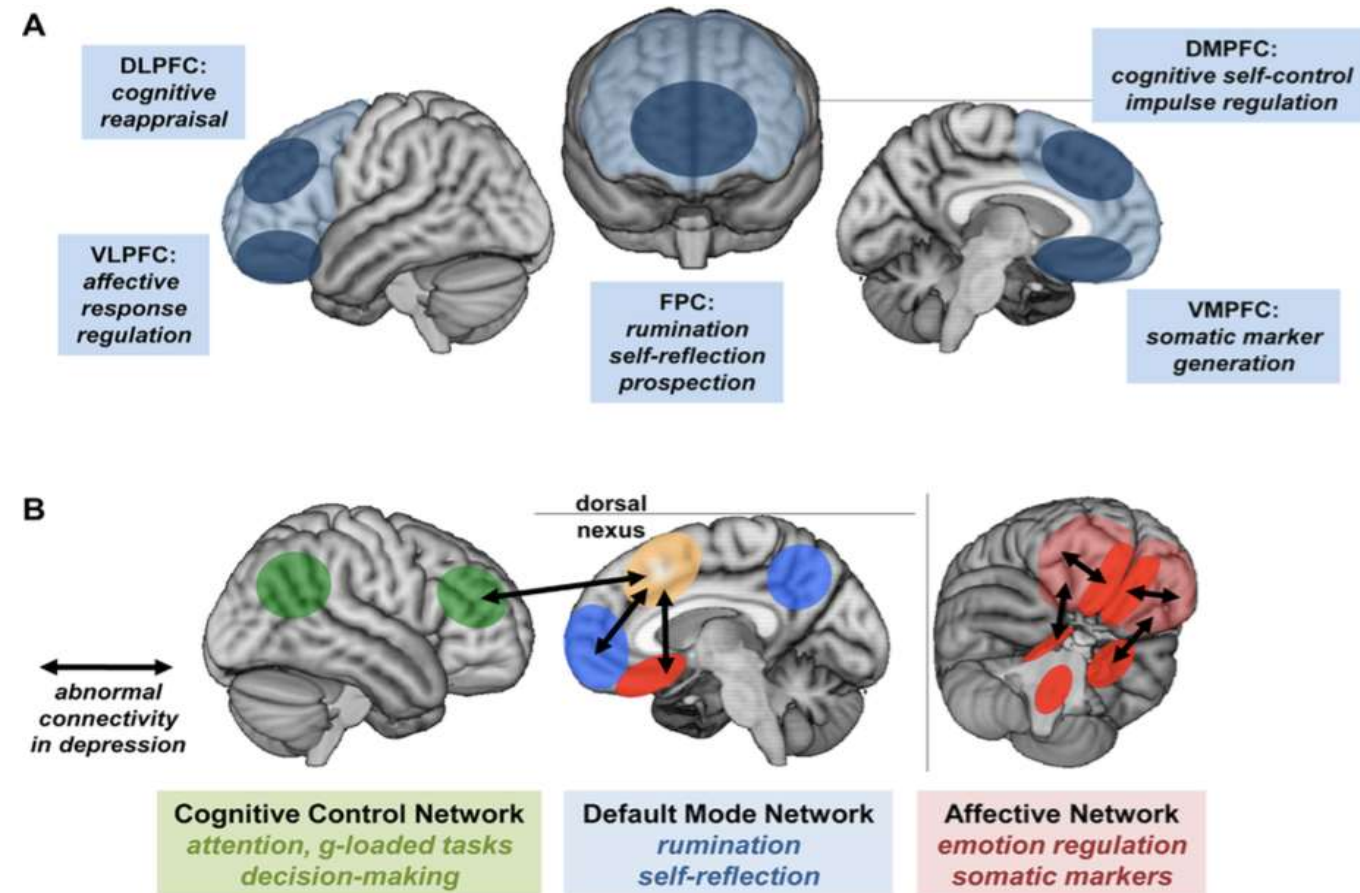


Cortical Entry Node: Site of Stimulation



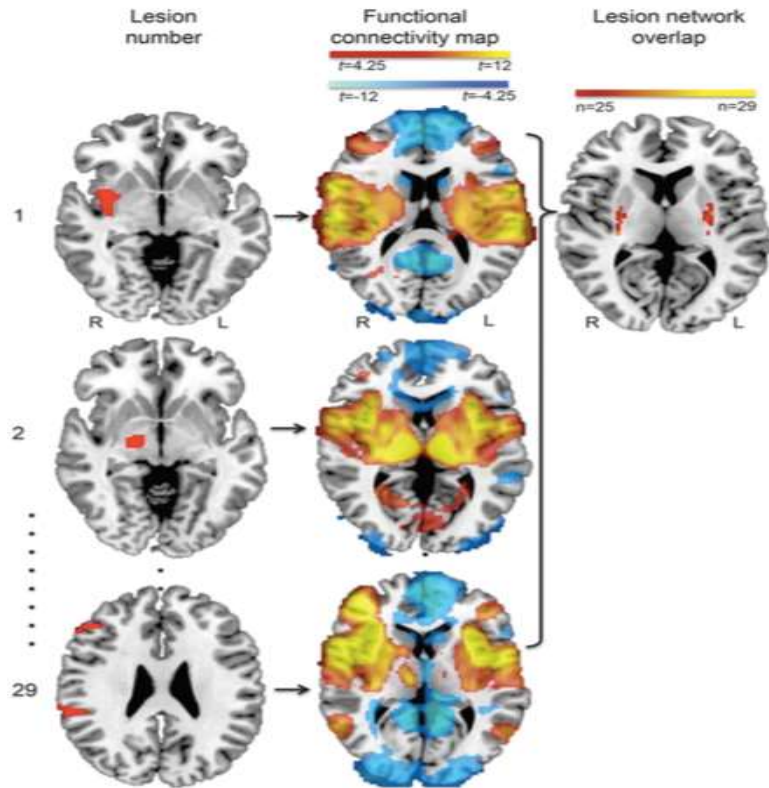
Cortical Entry Node: Based off of Lesion Studies

- There is one established target for depression, the L DLPFC.
- Inhibitory stimulation of the R DLPFC has strong data.
- DMPFC has + OL data.
- FPC has some emerging data.
- L DLPFC is the only target to do parameter development because it is an established target.



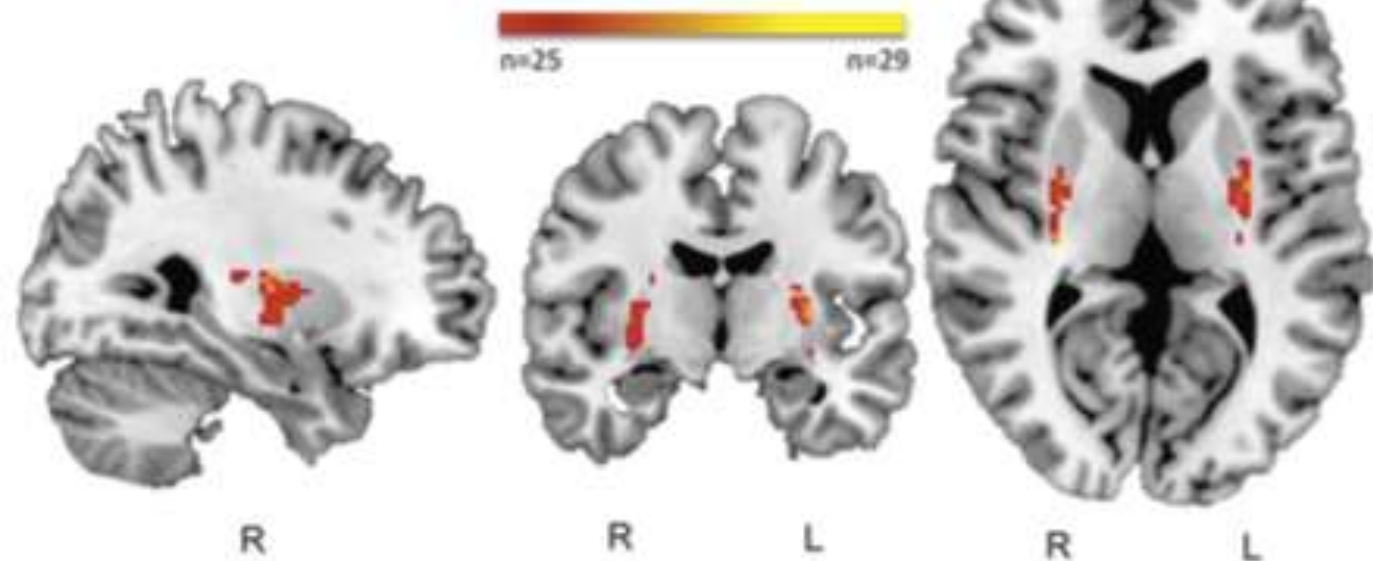
Network Localization Based On Lesions

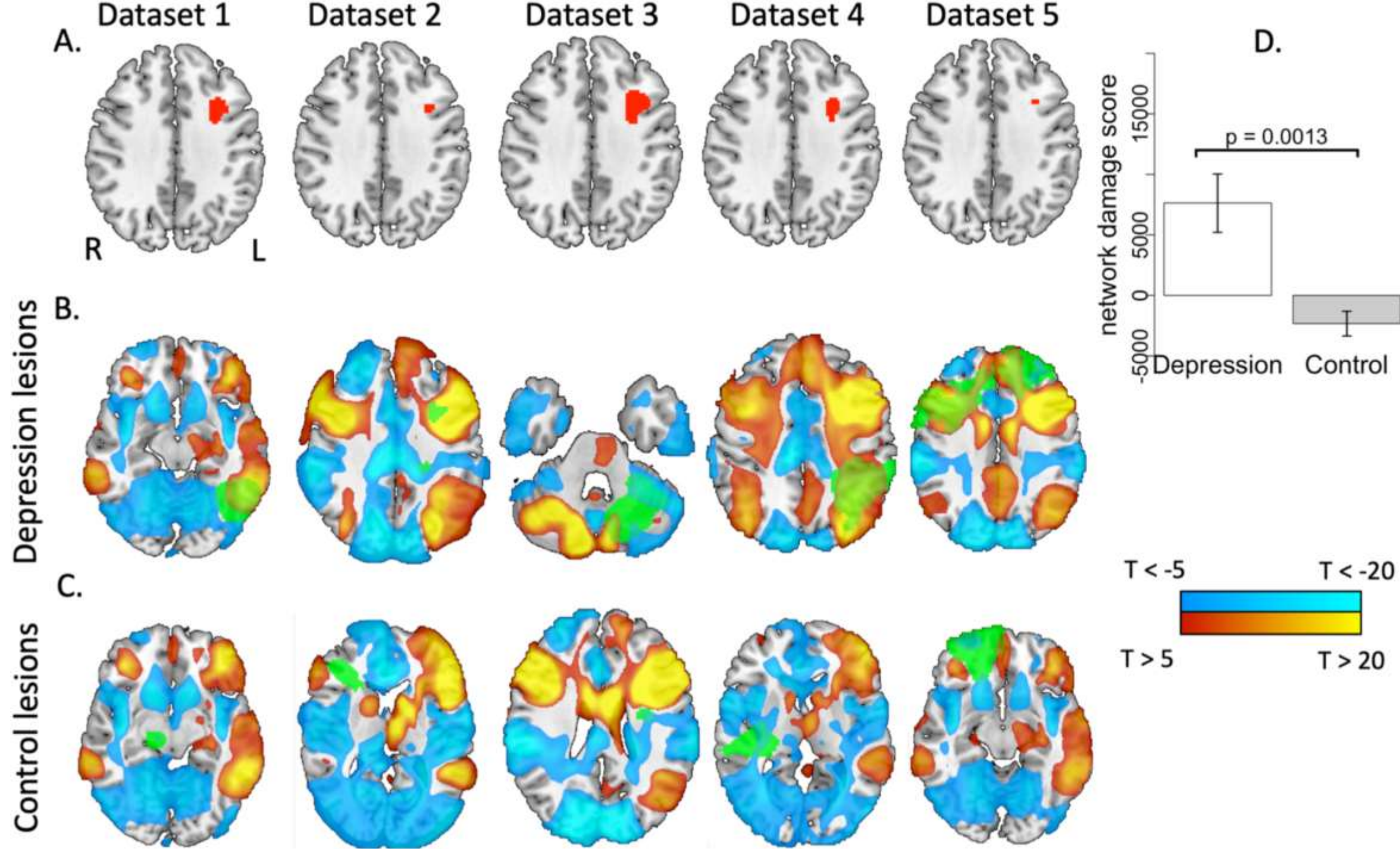
Lesion network mapping technique

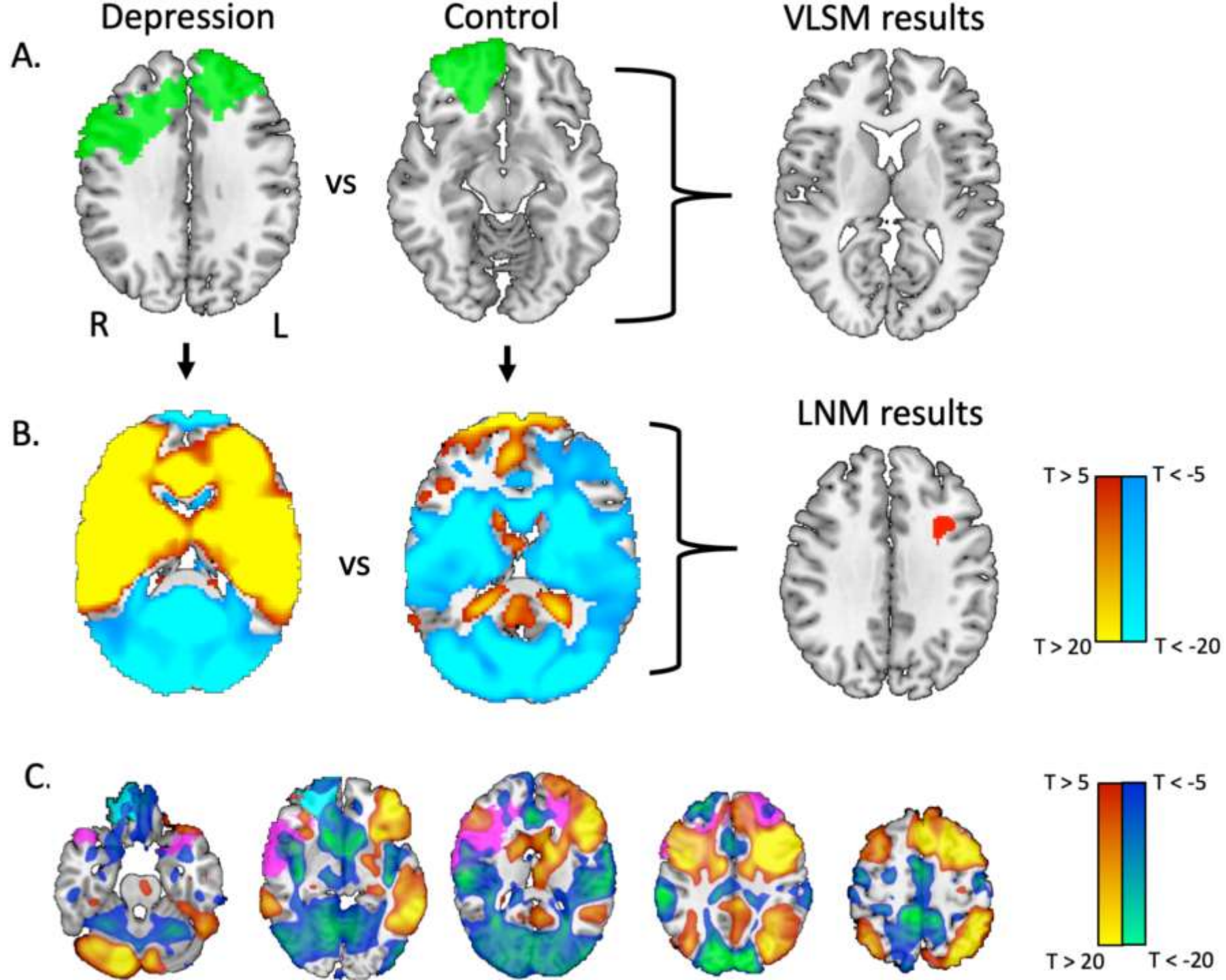


Hemichorea-hemiballismus lesions are functionally connected to the posterolateral putamen

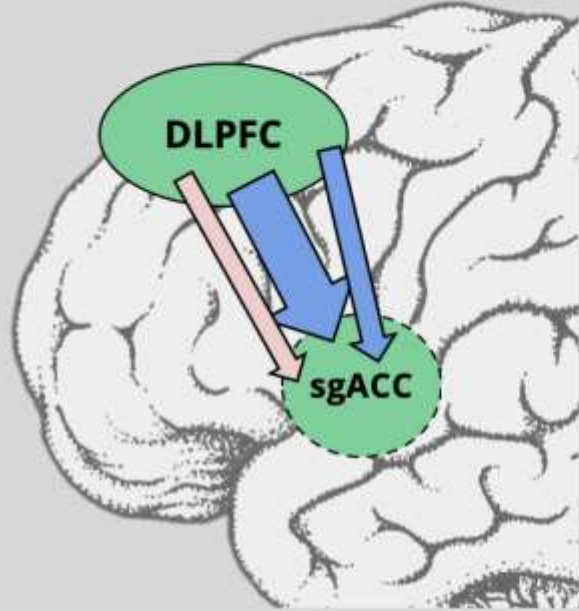
A. Functional connectivity overlap



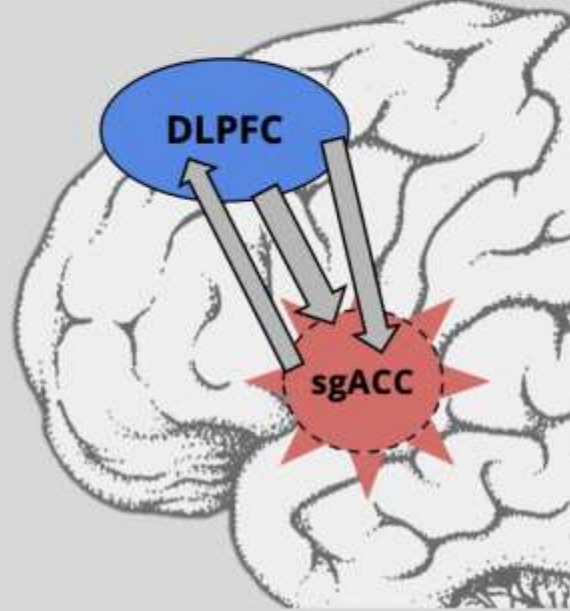




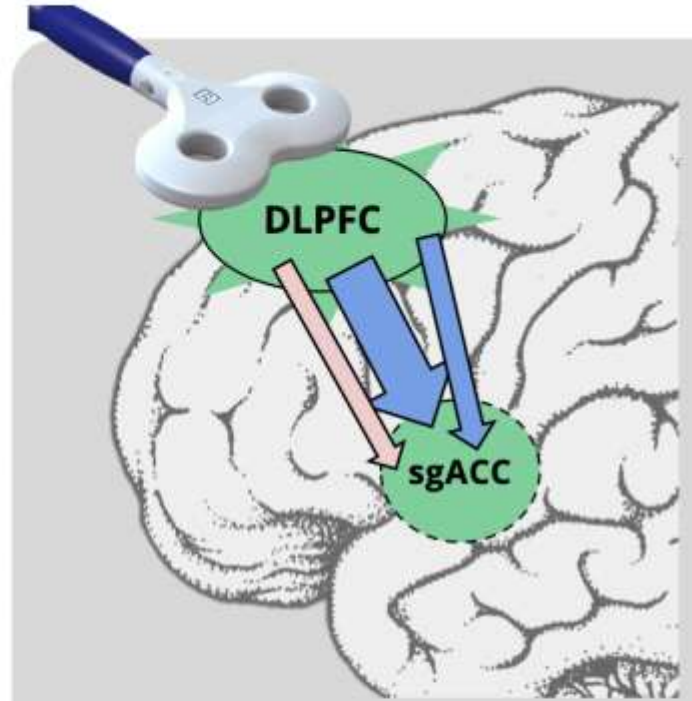
Biology of depression and TMS



The left dorsolateral prefrontal cortex (L-DLPFC) and subgenual cingulate (sgACC) are highly interconnected. Normally, DLPFC inhibits sgACC and mood is well-regulated.



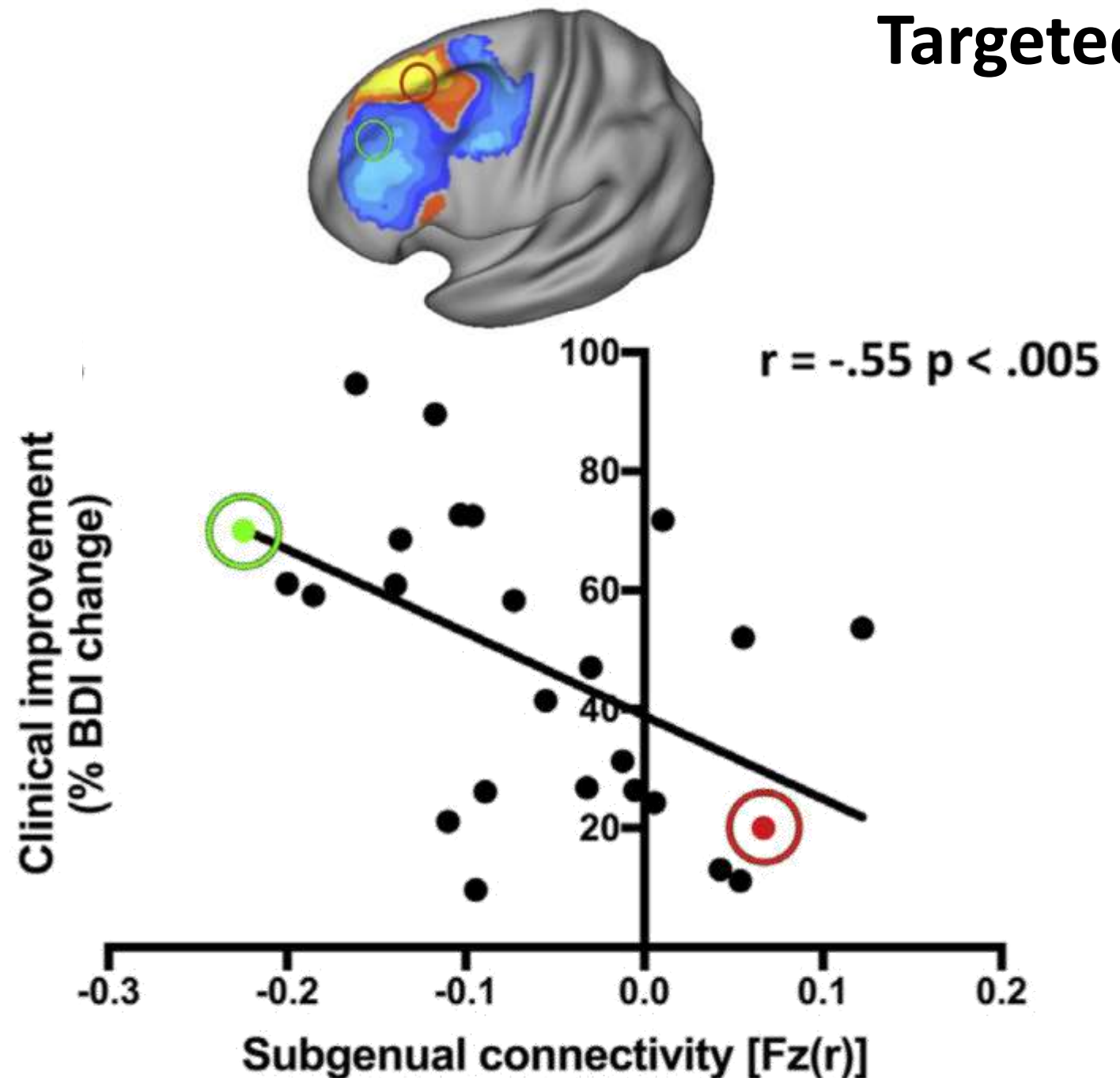
In MDD, DLPFC becomes less active and fails to inhibit sgACC. This network pathology, known for decades, causes cognitive impairment and inwardly directed negative thoughts (Baxter et al 1989, Drevets et al 1997).



TMS stimulates DLPFC, re-activating inhibitory connections to sgACC. This corrects the network imbalance and normalizes mood regulation (Liston et al 2015; Weigand et al 2017).

Negative connectivity between DLPFC and subgenual cingulate is associated with TMS efficacy

Weigand A, Horn A, Caballero R, Cooke D, Stern AP, Taylor SF, Press D, Pascual-Leone A, Fox MD. Prospective Validation That Subgenual Connectivity Predicts Antidepressant Efficacy of Transcranial Magnetic Stimulation Sites. Biol Psychiatry. 2017 Nov 10. PMID: 29274805



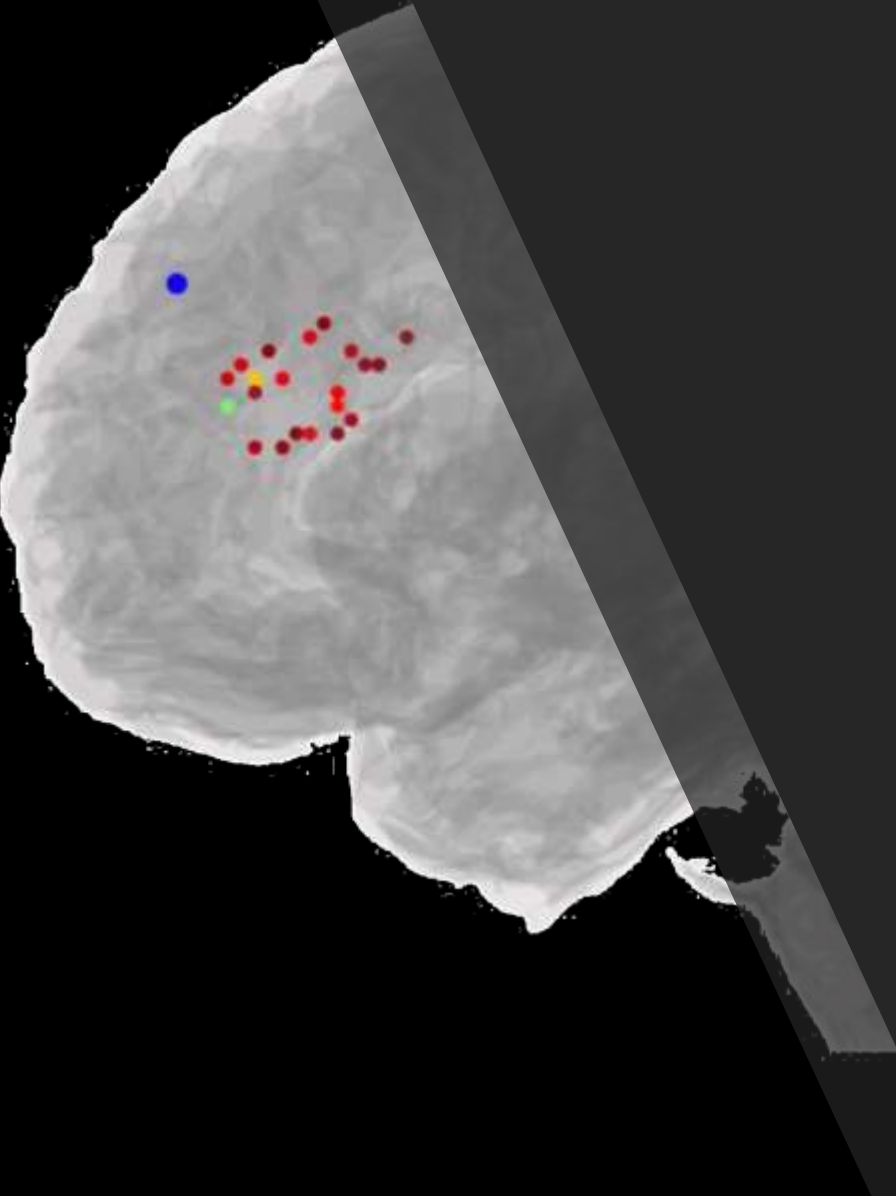
Protocol

Target

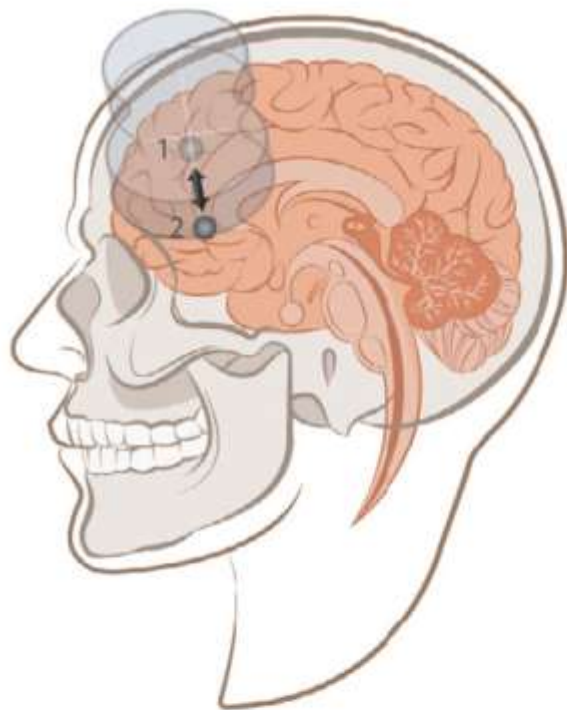
- Area of L-DLPFC with maximum negative connectivity with subgenual cingulate (resting state fcMRI)
- Neuronavigation equipment for targeting

Stimulation

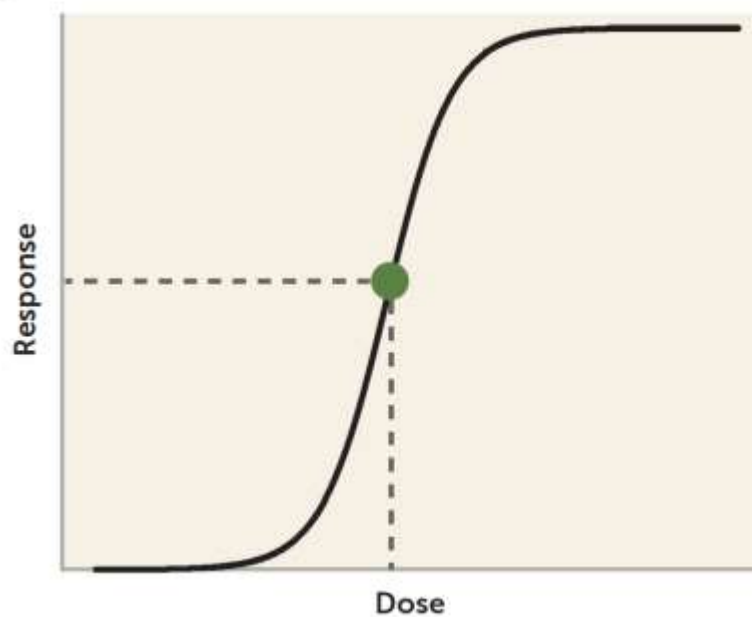
- Intensity: 90% RMT
- Pattern: iTBS (50Hz bursts at 5Hz, 2s trains, 8 second intervals)
- Session duration: 10 min = 1,800 pulses
- Sessions per day: 10, 1 session every 60 min (18,000 pulses per day)
- Days: 5 days (90,000 pulses total)



A



C



B

[illegible]

BRAIN

A JOURNAL OF NEUROLOGY

The American Journal of
Psychiatry

SAINT

Three clinical trials

- I. The **most** severely depressed and treatment-resistant patients
 - a. 5 of 6 patients in remission. 6th patient found to have primary OCD
- II. Open-label trial in treatment-resistant depression
 - a. 19 of 21 patients in remission.

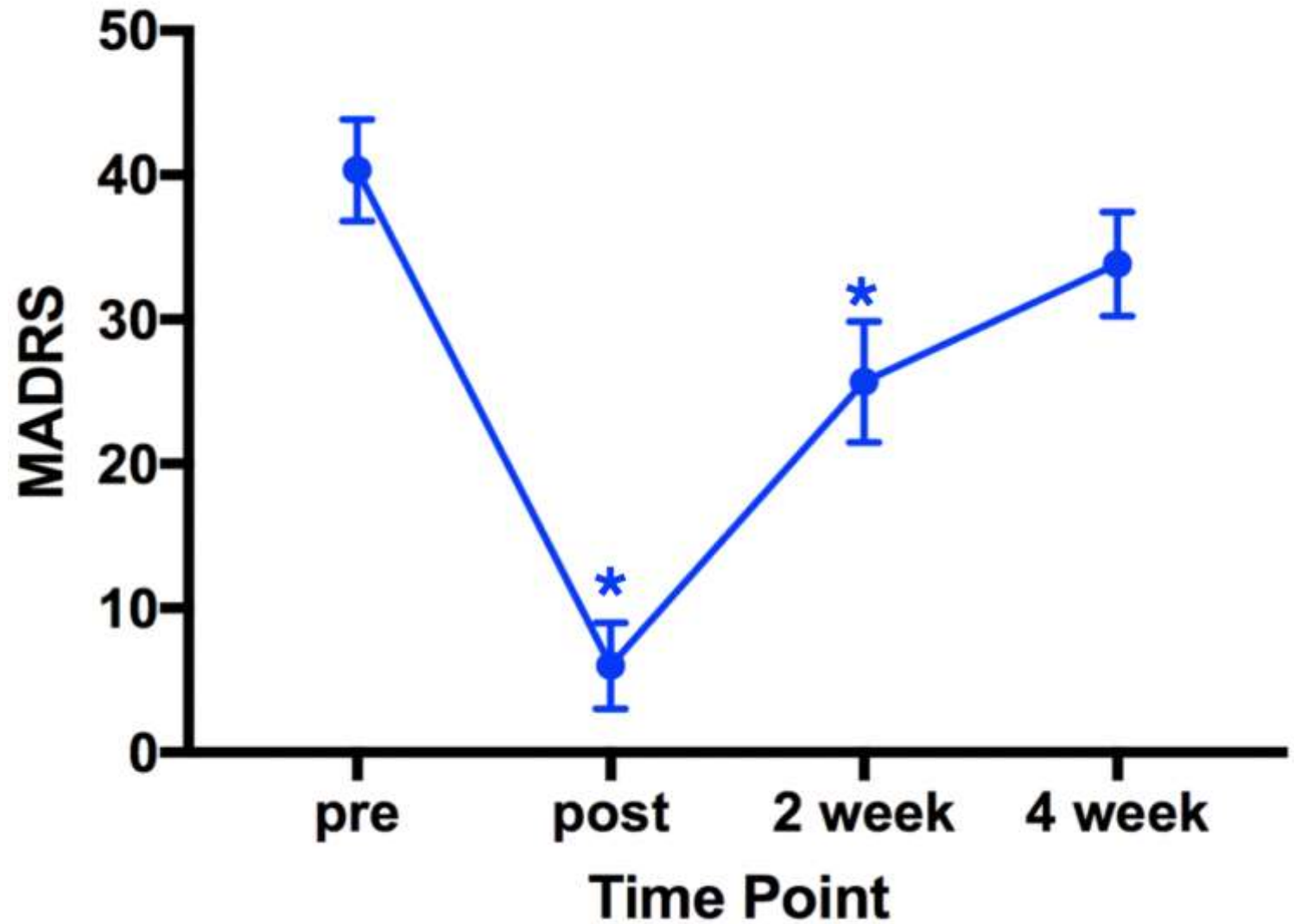
Is this all a powerful sham effect?

Brain Letter

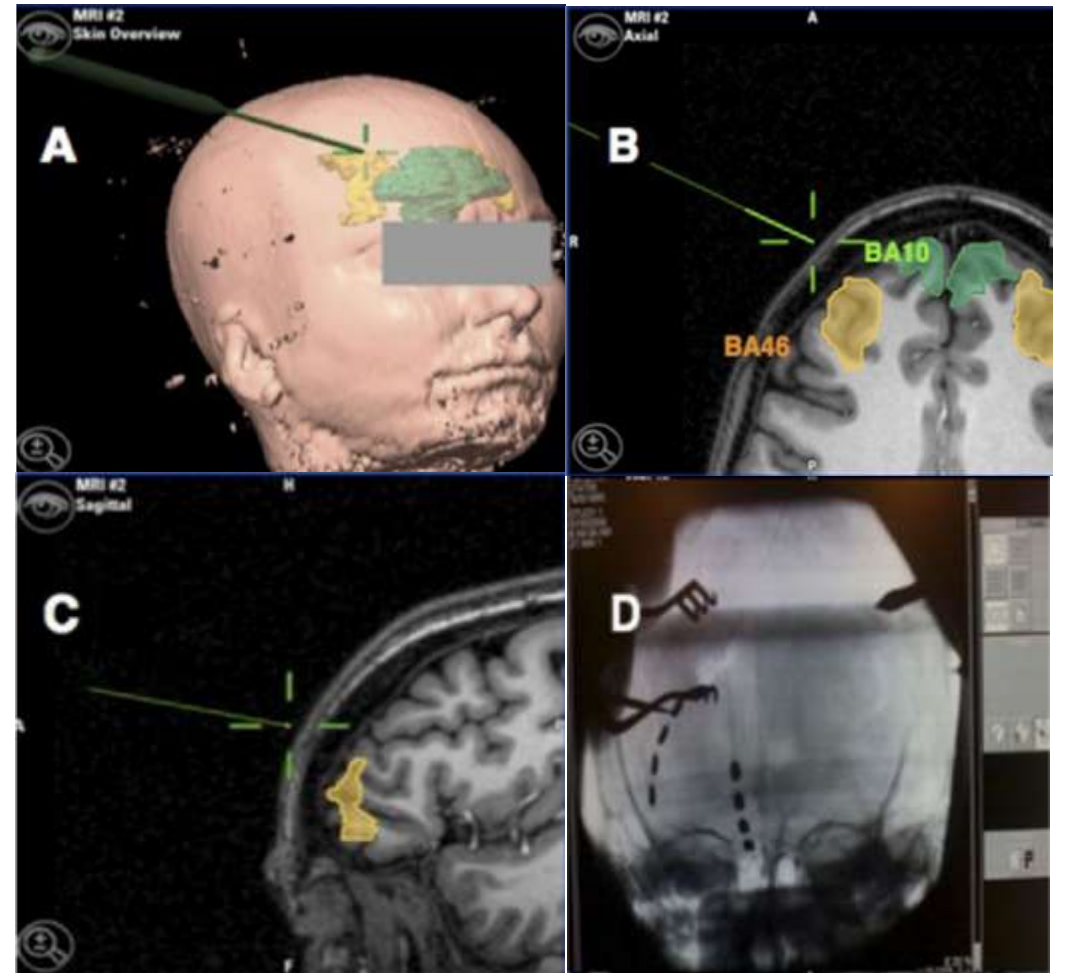
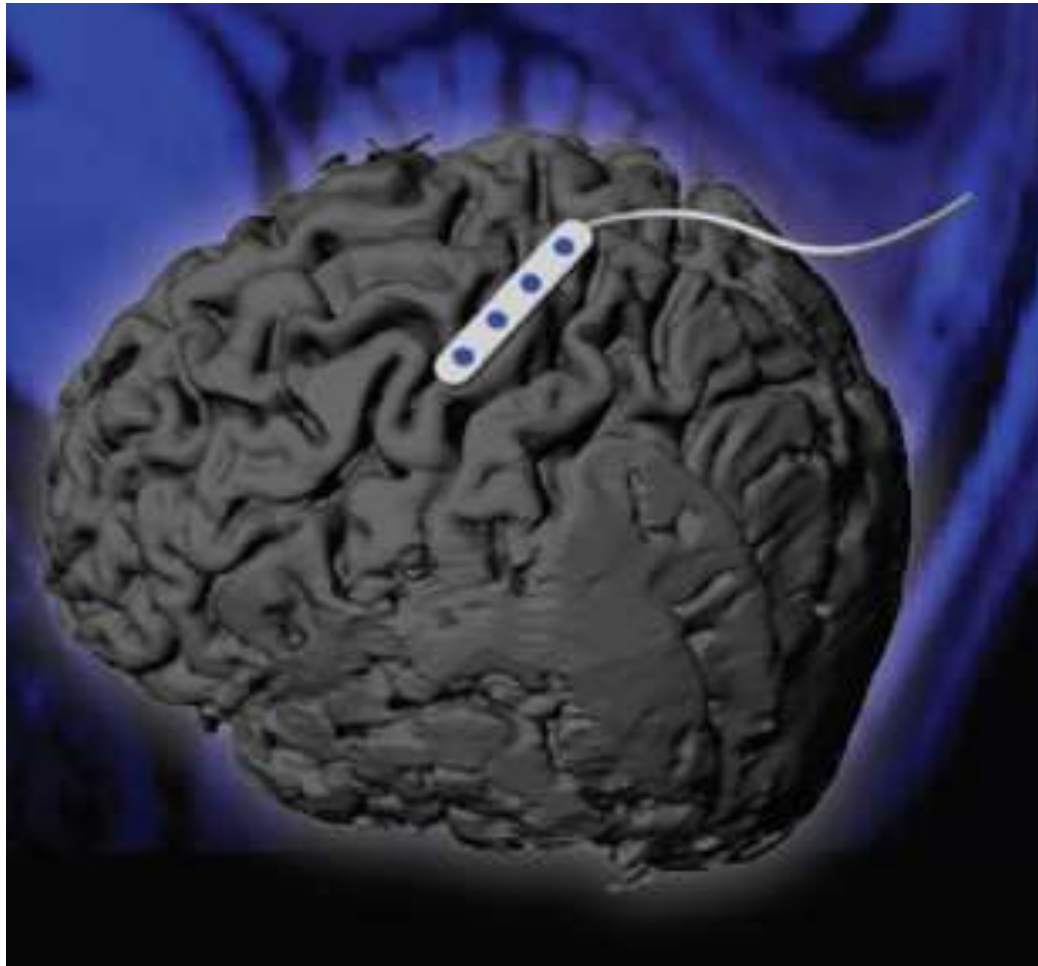
Surgical- Level Depression

	Participant ID						Group
	1	2	3	4	5	6	
General characteristics							
Gender	M	F	F	F	M	F	4 F/2 M
Diagnosis at entry	MDD	BPAD Depressed	MDD	MDD	MDD ^b	MDD	5 MDD/1 BPAD
Age at treatment	69	53	66	47	63	38	56 (±12.1)
Education (years)	14	15	16	19	19	22	17.5 (±3.0)
Unemployed/functionally disabled	Y	Y	Y	Y	Y ^a	Y	All
Psychiatric history							
Age at MDD onset	32	18	20	18	33	23	24 (±6.8)
Length of illness (years)	37	35	46	29	30	15	32 (±10.3)
Current depressive apisode (years)	27	15	9	15	8	15	14.8 (±6.8)
Family history of MDD	Y	Y	Y	N	Y	N	4 Y/2 N
Psychiatric hospitalizations	0	5	1	0	2	7	2.5 (±2.9)
Treatment resistance							
Maudsley Staging Method	14	14	14	14	14	14	14
Thase and Rush Staging Method	5	5	5	5	5	5	5
Previous brain stimulation therapy failure							
VNS	Y	N	N	N	N	N	1 Y/5 N
ECT (courses)	1	2	1	1	1	1	1.2 (±0.4)
Right unilateral (total sessions)	0	12	12	10	15	0	8.2 (±6.5)
Bilateral (total sessions)	20	28	28	0	18	16	18.3 (±10.3)
TMS (courses)	2	1	2	2	1	2	1.7 (±0.5)
TMS (average sessions per course)	26	37	39.5	30.5	25	25	30.5 (±6.4)
DBS consultation	Y	N	N	Y	Y	Y	4 Y/2 N
Psychotherapy failure	Y	Y	Y	Y	Y	Y	All
Ketamine failure	Y	N	N	Y	Y	Y	4 Y/2 N

aTBS Patients Meeting DBS Criteria



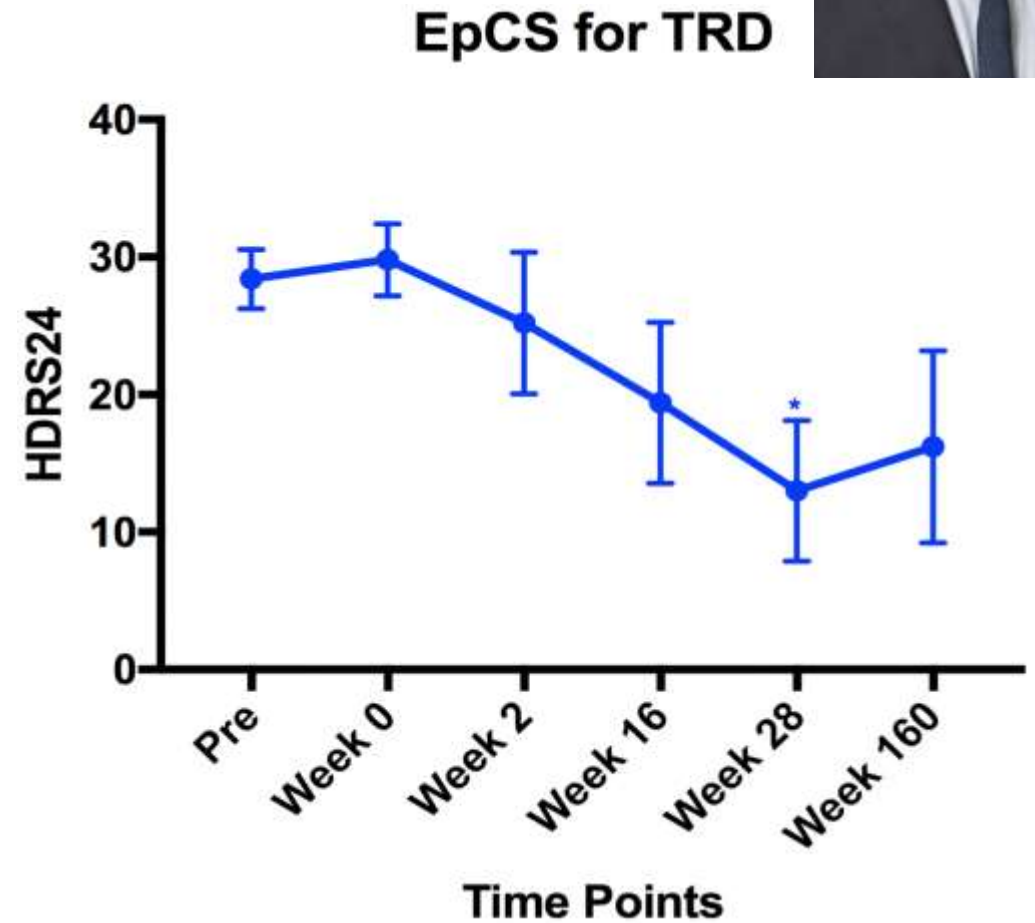
Epidural Prefrontal Cortical Stimulation (EpCS)



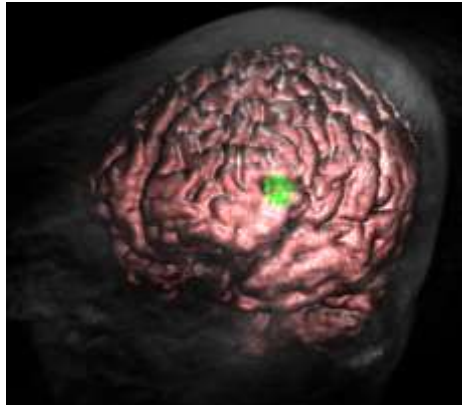
Results for EpCS patients



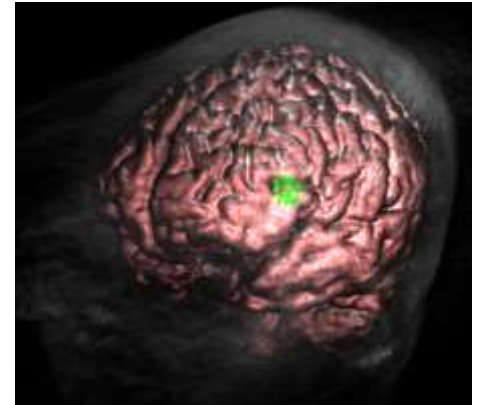
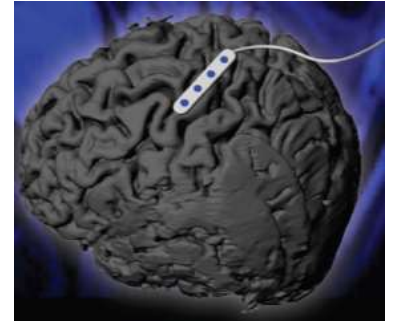
	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Group
Gender	F	M	F	F	F	4 F/1 M
Diagnosis recurrent	MDD	BPAD depressed	BPAD depressed	Recurrent MDD	Recurrent MDD	3 MDD/2 BPAD
Current age	42	57	47	31	45	44.4 (± 9.7) ^b
Length of illness (years)	17	32	31	16	32	25.6 (± 8.3)
Current depressive episode (months)	N/A	N/A	84	8	N/A	46 (± 53.7)
HRSD score (24 item)	23	33	33	29	24	28.4 (± 8)
Previous brain stimulation therapies	ECT, VNS, TMS	ECT, VNS, TMS	ECT	VNS, TMS	None	4 yes/1 no
Past psychotherapy	Yes	Yes	Yes	Yes	Yes	All
Family history of depression	Yes	Yes	No	Yes	Yes	4 yes/1 no
Number of psychiatric treatments in current depressive episode ^a	12	18	6	8	5	9.8 (± 5.3)
Current ATHF	8	8	4	5	4	5.8 (± 2.05)
Number of psychotropics at baseline	9	5	6	3	7	6 (± 2.23)
Number of psychotropics at 5 years	5	2	5	5	5	4.4 (± 1.34)



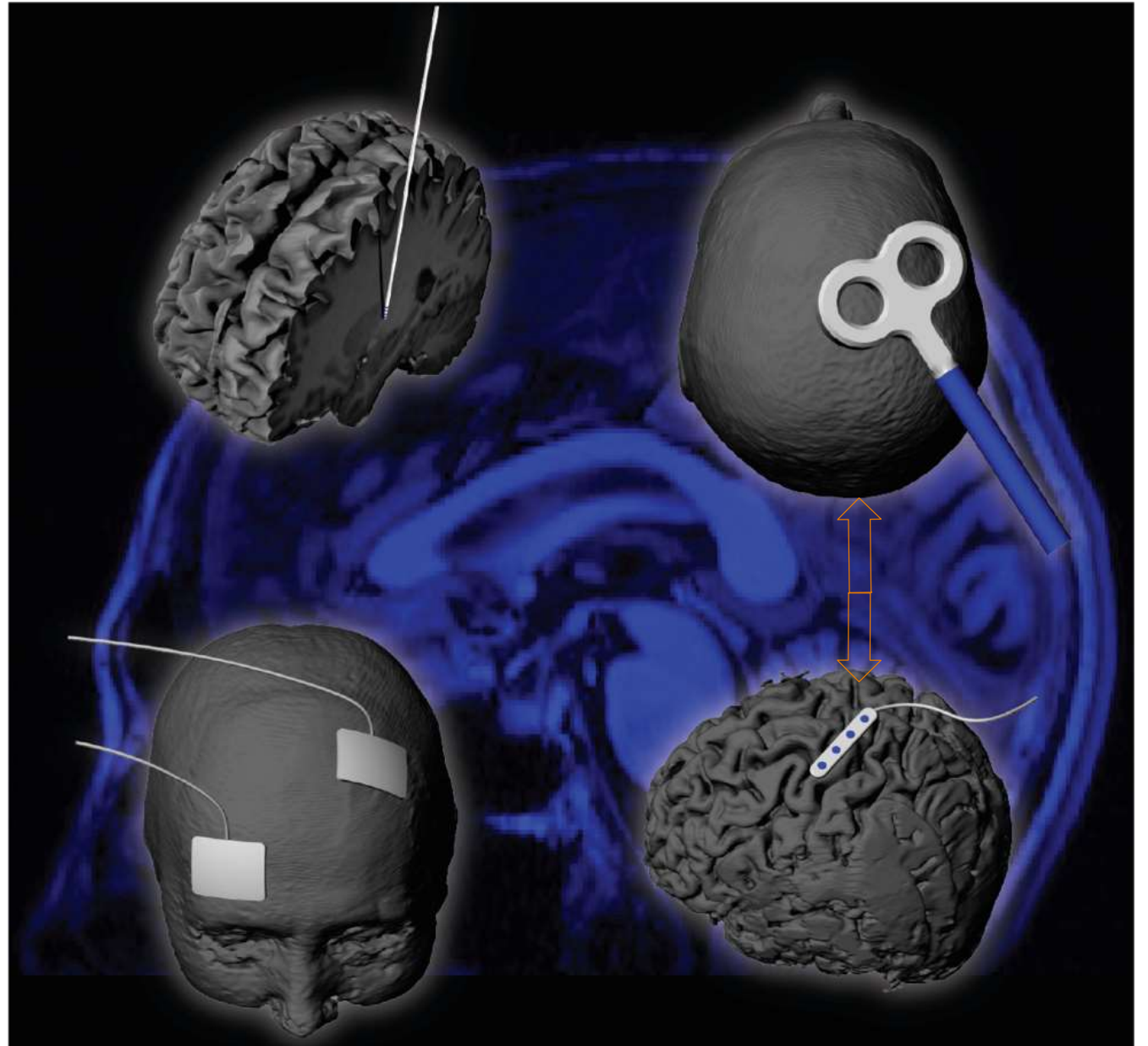
Epidural Prefrontal Cortical Stimulation 2.0

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Non-Invasive and Invasive Brain Stimulation Inform Each Other



AJP Paper

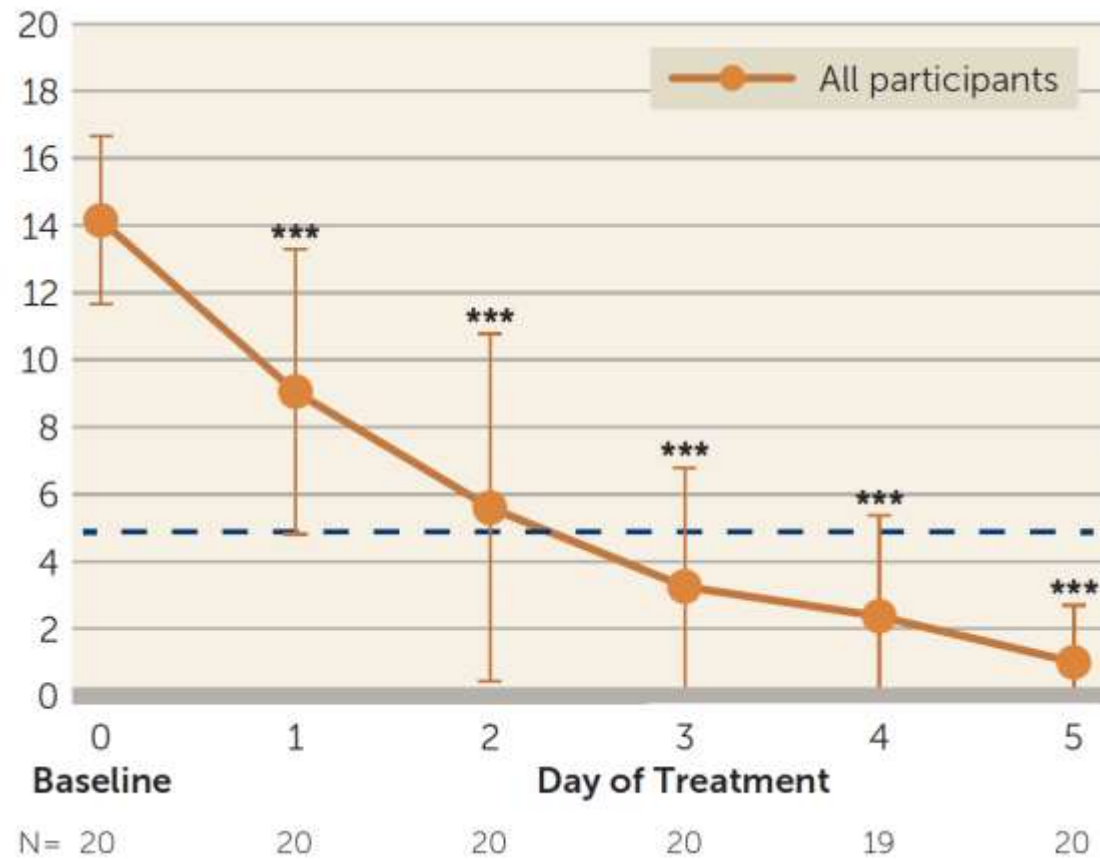
Demographics

Characteristic or Measure		
	Mean	SD
Age (years)	44.86	17.21
Age at onset of depression (years)	21.90	13.11
Duration of depression (years)	22.95	16.30
Number of adequate antidepressant trials (lifetime) ^b	5.86	3.53
Number of adequate adjunctive medications (lifetime) ^c	1.10	0.94
Maudsley Staging Method	10.14	1.96

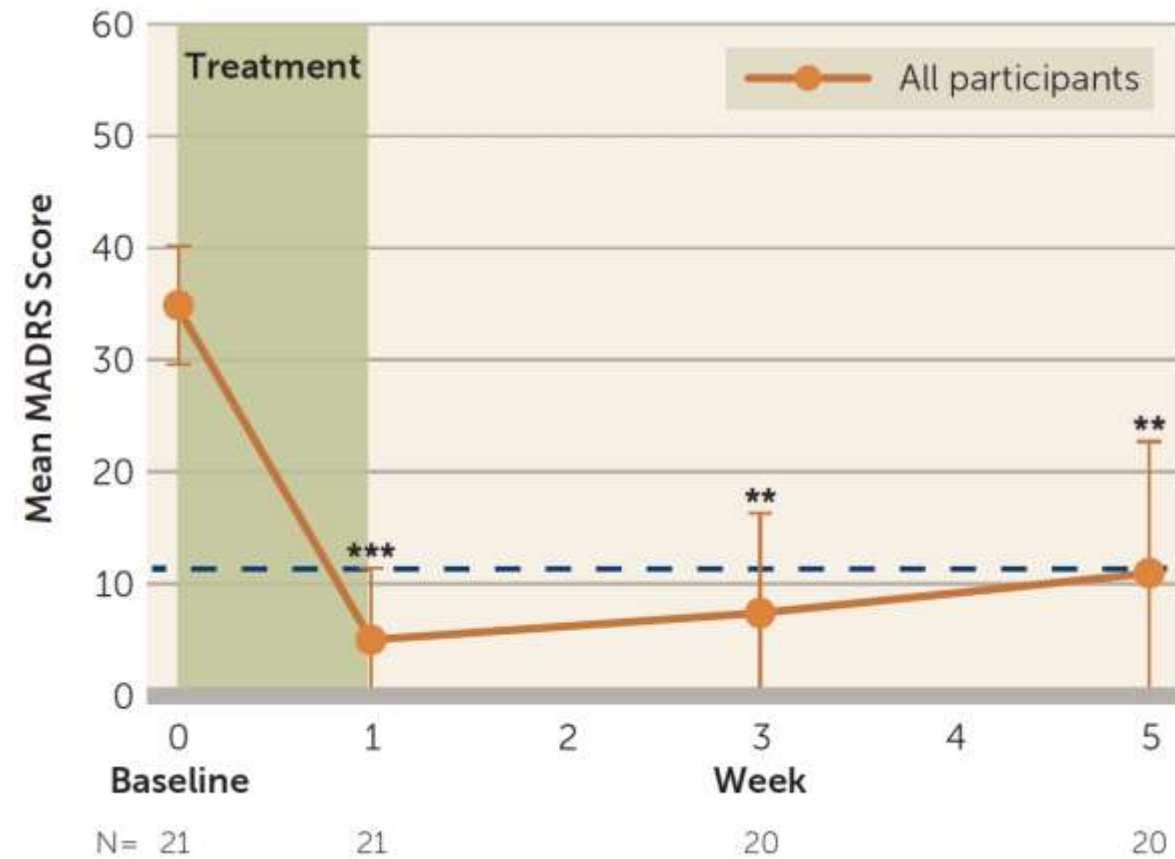
	N	% ^a		Mean	SD
Female	12	57.1	Baseline clinical measures		
Participants who failed adequate medication trials ^b			MADRS	34.86	5.29
1–2 trials	2	9.5	HAM-D, 17-item	25.90	4.79
3–4 trials	7	33.3	HAM-D, 6-item	13.90	2.45
5–6 trials	3	14.3	BDI-II (N=18)	28.78	11.68
7–10 trials	7	33.3	Suicidal ideation		
>10 trials	2	9.5	C-SSRS, suicidal ideation subscale (N=19)	1.42	0.96
Participants who attempted FDA-approved rTMS	7 ^d	33.3	HAM-D, item 3	1.38	0.67
Participants who attempted ECT	0	0.0	MADRS, item 10	2.38	0.80

Results

A

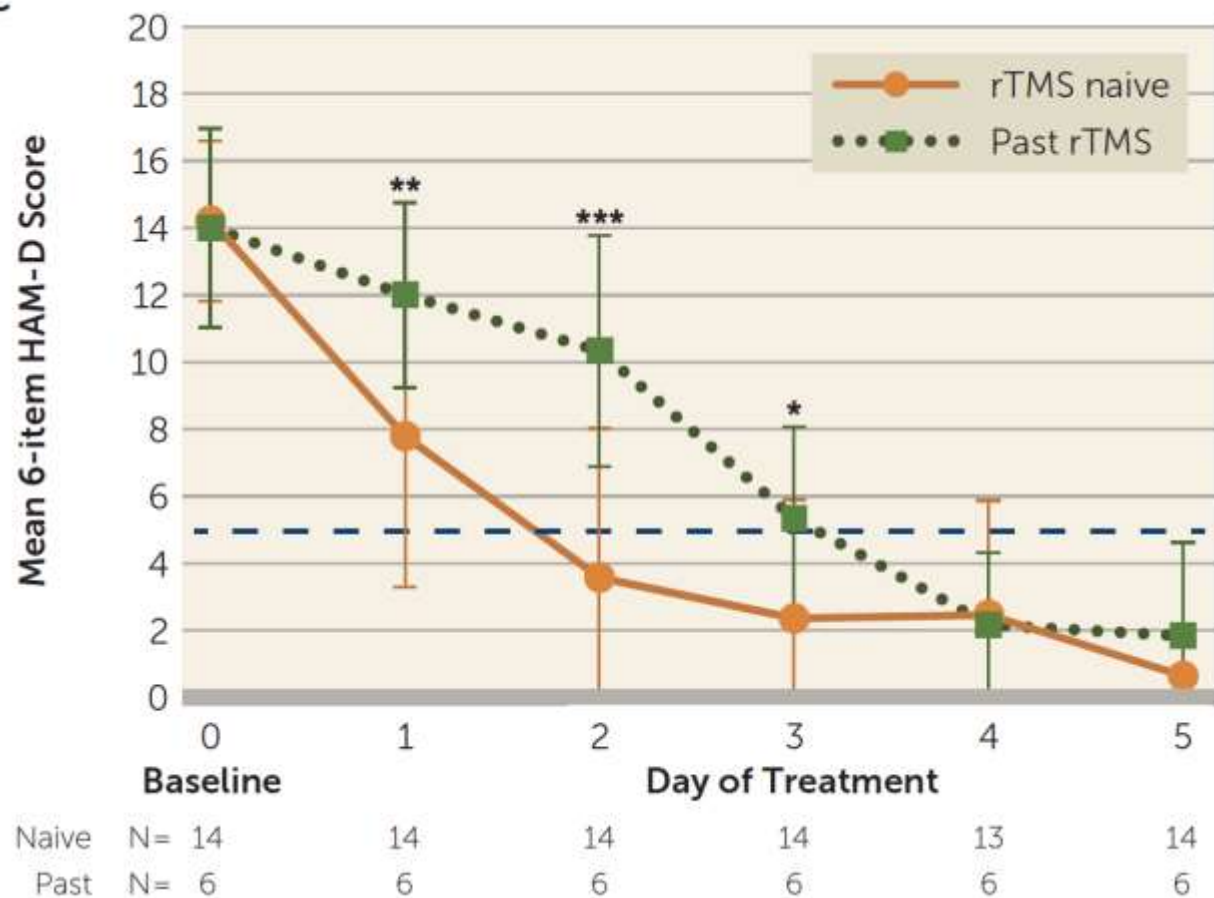


B

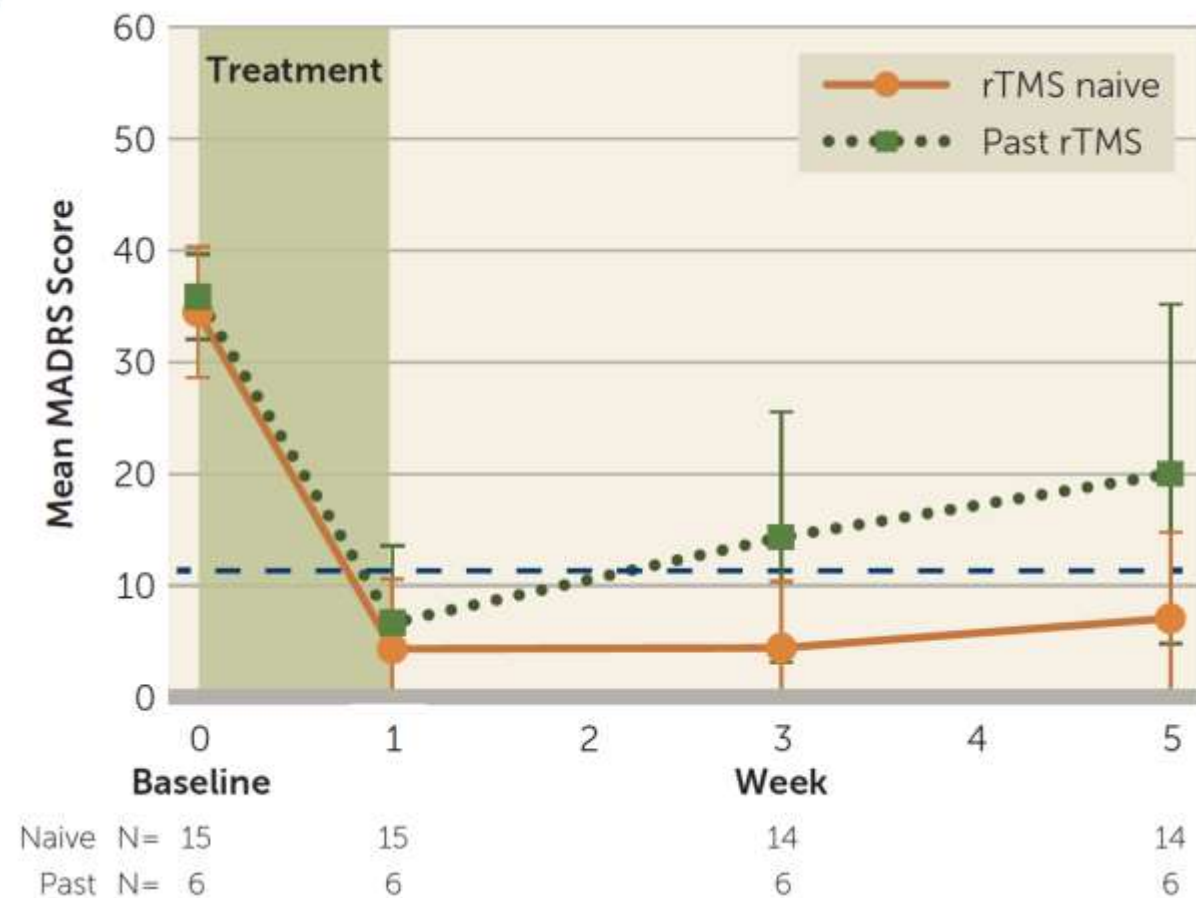


Results

C

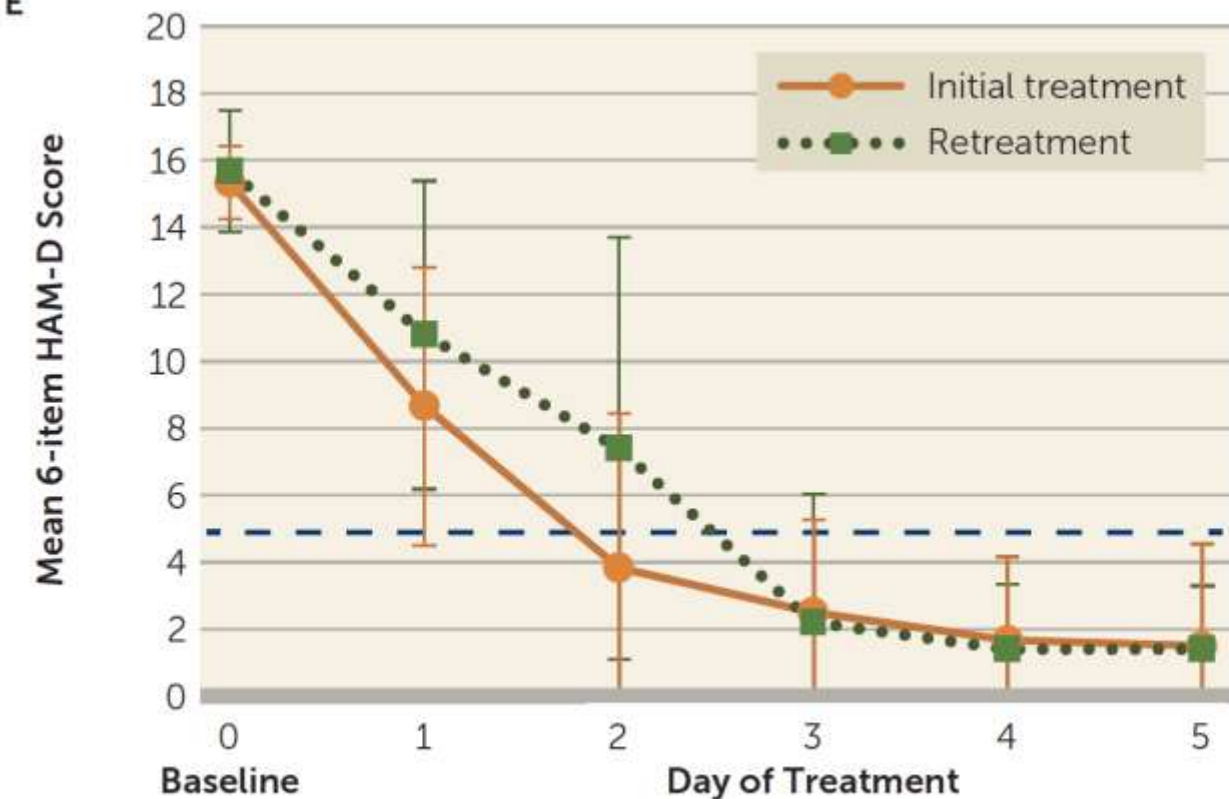


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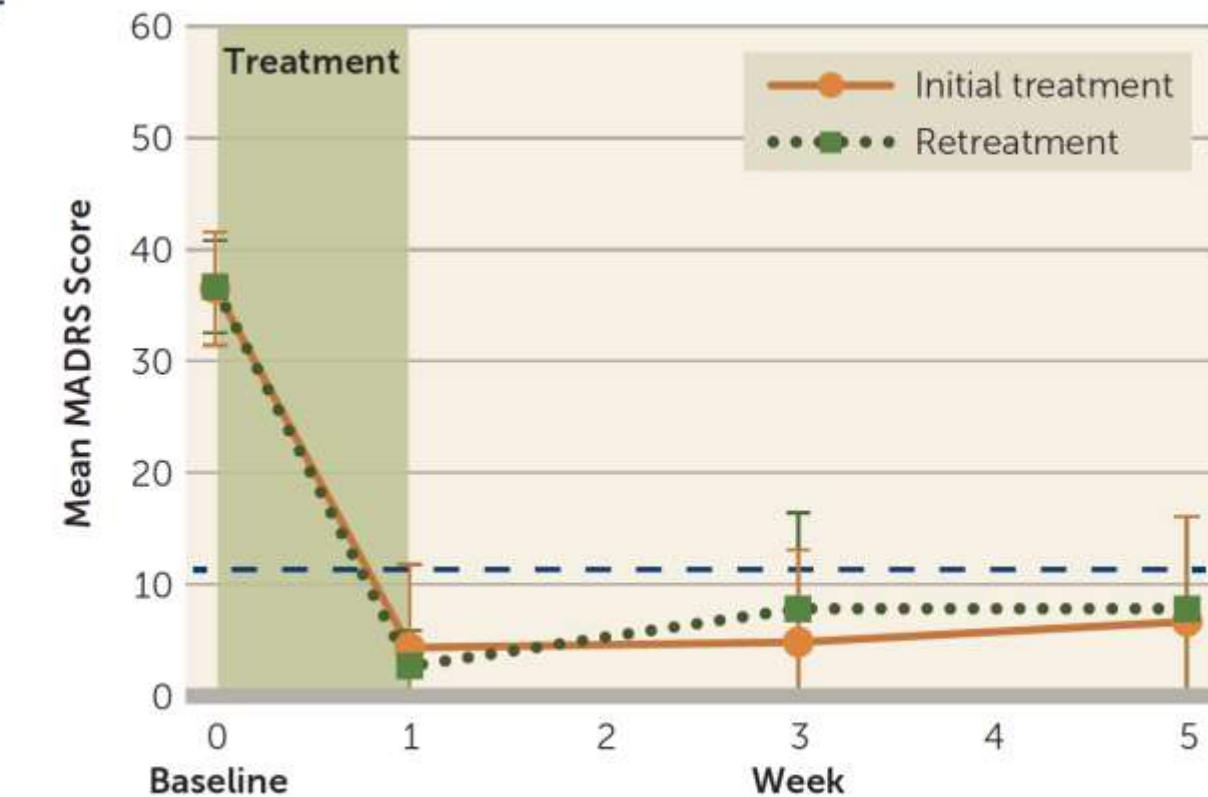
Results

E



Initial	N=	6	6	6	6	6	6
Repeat	N=	6	5	5	5	5	5

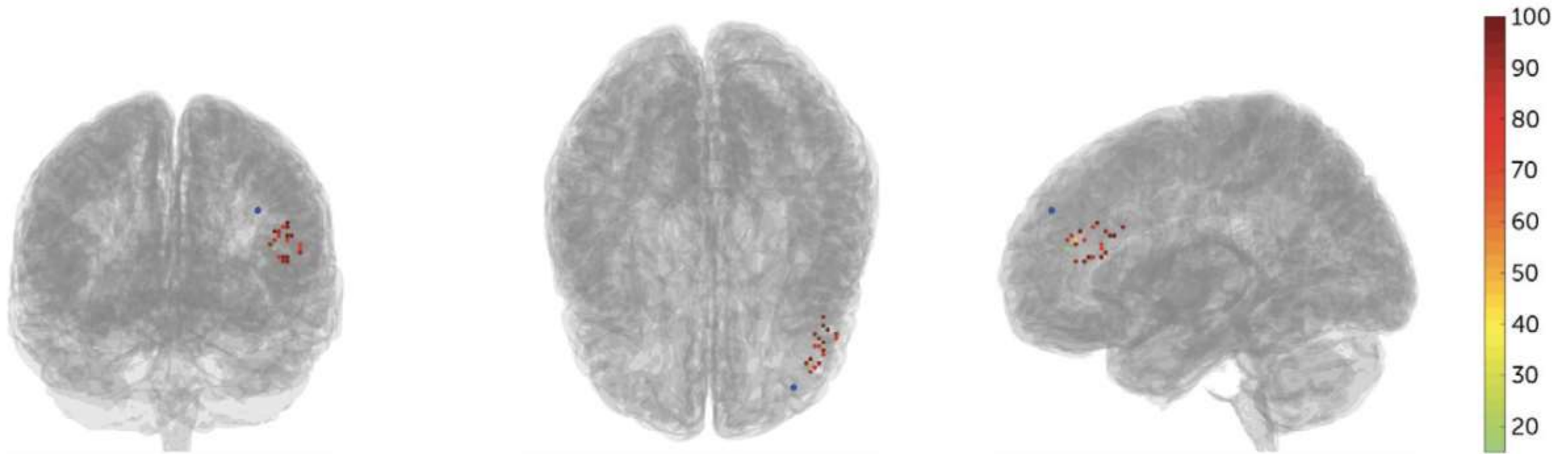
F



Initial	N=	6	6	6	6
Repeat	N=	6	6	6	6

Results

FIGURE 2. Individual target locations used in this study of Stanford Accelerated Intelligent Neuromodulation Therapy in comparison to the average coordinates for the F3 location in the 10-20 system^a



^a The average F3 location (at MNI coordinates -35.5, 49.4, 32.4) is shown in blue (78). The colors of the targets represent the percent change in Montgomery-Åsberg Depression Rating Scale score, with dark red indicating greater change. The mean distance from F3 was 25.18 mm (SD=6.15).

Brain Stimulation Lab

