Interventional Psychiatry

Nolan Williams MD

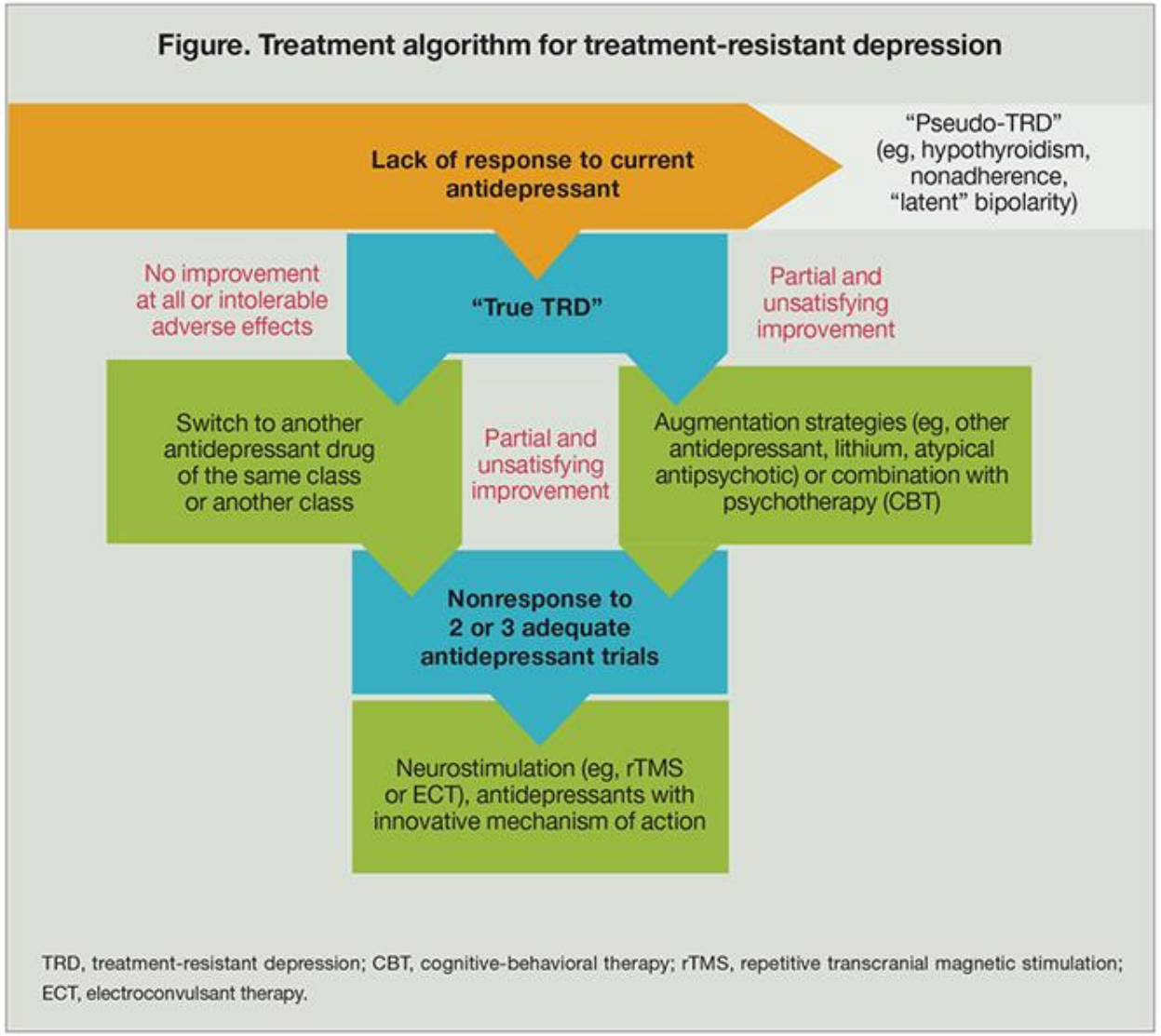
Director, Stanford Brain Stimulation Lab

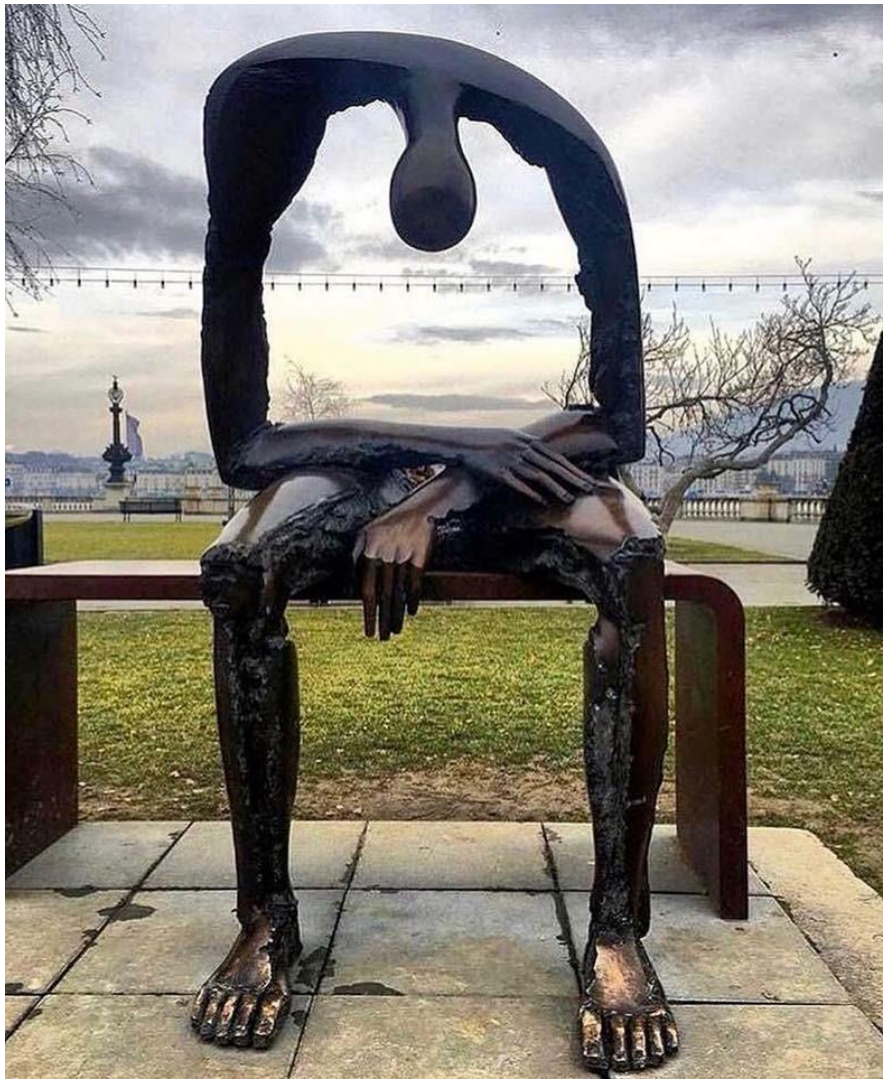
Director, Stanford Interventional Psychiatry Research

Disclosures

- On the advisory boards for Otsuka, NeuraWell, Magnus, Nooma, and Halo Neuroscience.

Current State of the Art for TR Depression





Melancholy by Albert György

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

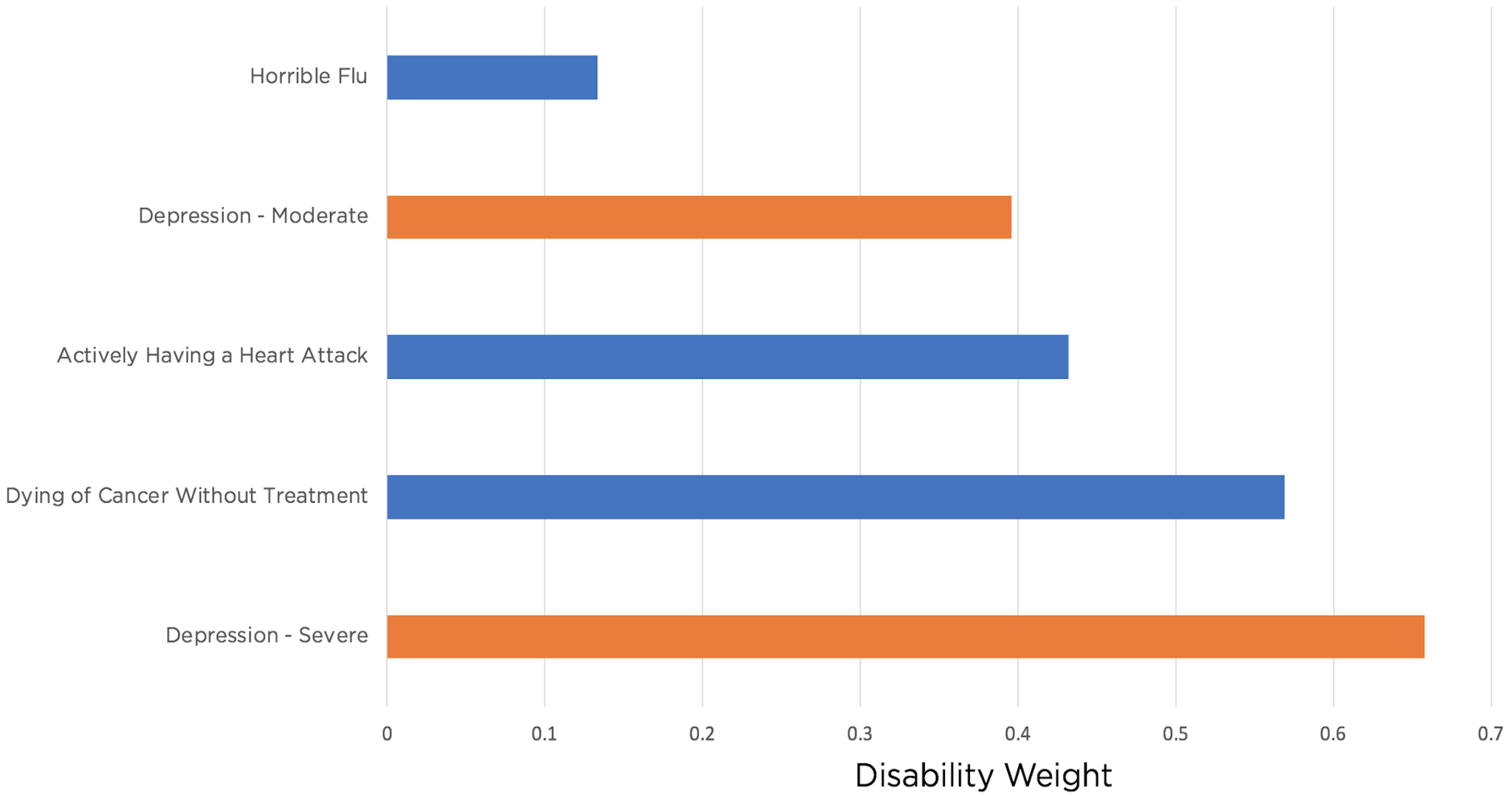
Economic burden of depression in America is over $210B annually

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)

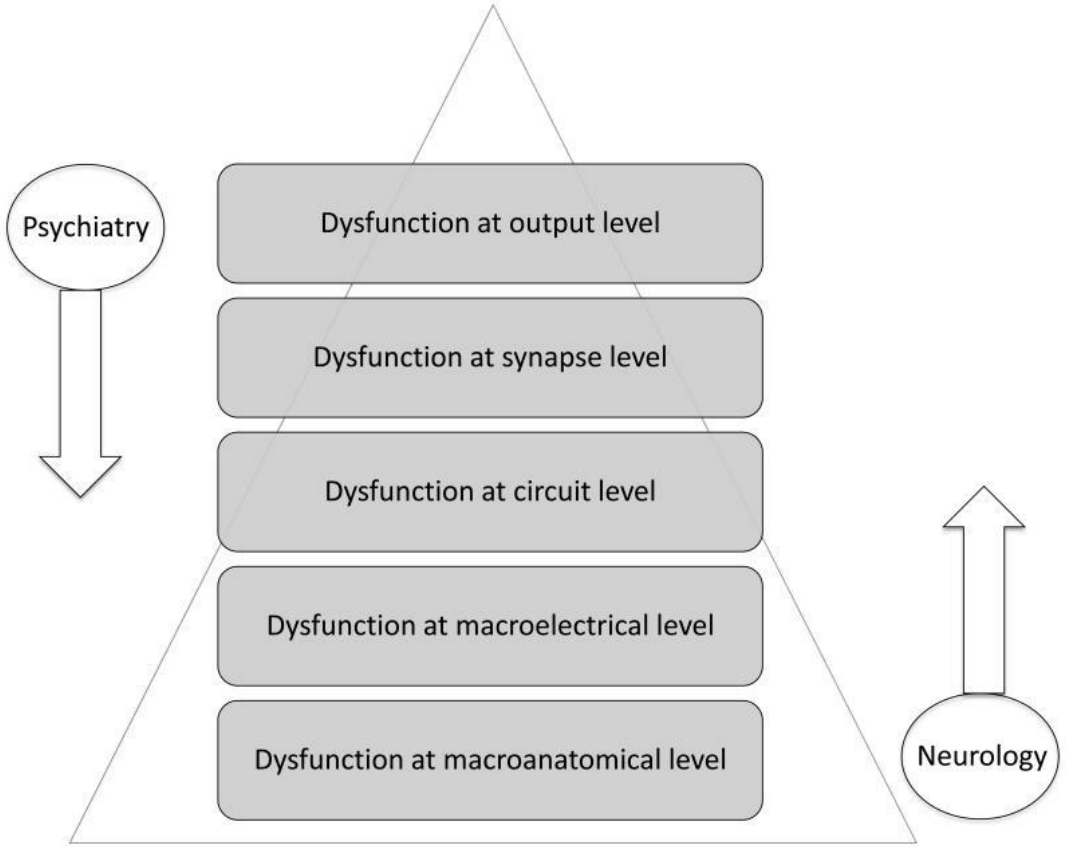
Antidepressants do not affect suicidality



Lancet Glob Health 2015. 3:e712-23

- **Psychiatry 1.0**
- Era of Mental Content
- Psychotherapy

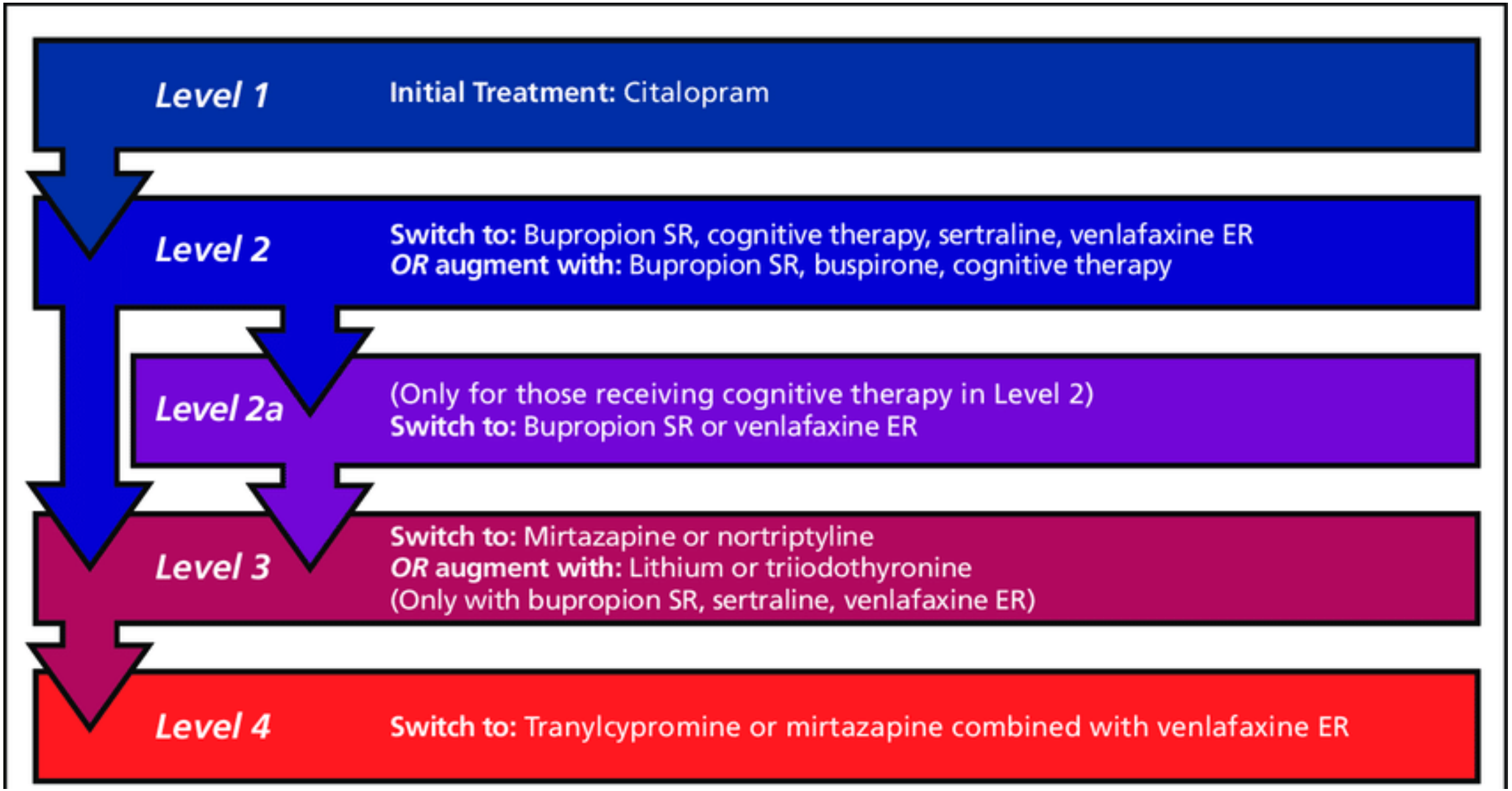
- **Psychiatry 2.0**
- Era of the Synapse
- Psychopharmacology



- **Psychiatry 3.0**
- Era of Brain Circuitry
- Circuit targeted modulation
- Encompasses and transforms our understanding of Psychiatry 1.0 and 2.0 through brain circuitry
- Interventional Psychiatry

Taylor, Williams, George 2016


PSYCHIATRY


Level 1
Initial Treatment: Citalopram
Level 2
Switch to: Bupropion SR, cognitive therapy, sertraline, venlafaxine ER
OR augment with: Bupropion SR, buspirone, cognitive therapy
Level 2a
(Only for those receiving cognitive therapy in Level 2)
Switch to: Bupropion SR or venlafaxine ER
Level 3
Switch to: Mirtazapine or nortriptyline
OR augment with: Lithium or triiodothyronine
(Only with bupropion SR, sertraline, venlafaxine ER)
Level 4
Switch to: Tranylcypromine or mirtazapine combined with venlafaxine ER

- **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

	Intention-to-Treat Sample				Per Protocol Sample			
	rTMS (N=48)		Medication (N=41)		rTMS (N=44)		Medication (N=32)	
Rate	N	%	N	%	N	%	N	%
Hamilton Depression Rating Scale								
Response rate	18	37.5	6	14.6	18	40.9	6	18.8
Remission rate	13	27.1	2	4.9	13	29.5	2	6.3
Beck Depression Inventory								
Response rate	16	33.3	3	7.3	16	36.4	3	9.4

Interventional Psychiatry: Why Now?

Nolan R. Williams, MD[1,2], **Joseph J. Taylor, PhD**[1,2], **Suzanne Kerns, MD**[1], **E. Baron Short, MD, MSCR**[1], **Edward M. Kantor, MD**[1], and **Mark S. George, MD**[1,2,3]

[1]Department of Psychiatry, Medical University of South Carolina

[2]Department of Neurosciences, Medical University of South Carolina

[3]Ralph H. Johnson VA Medical Center, Charleston, SC

Introduction

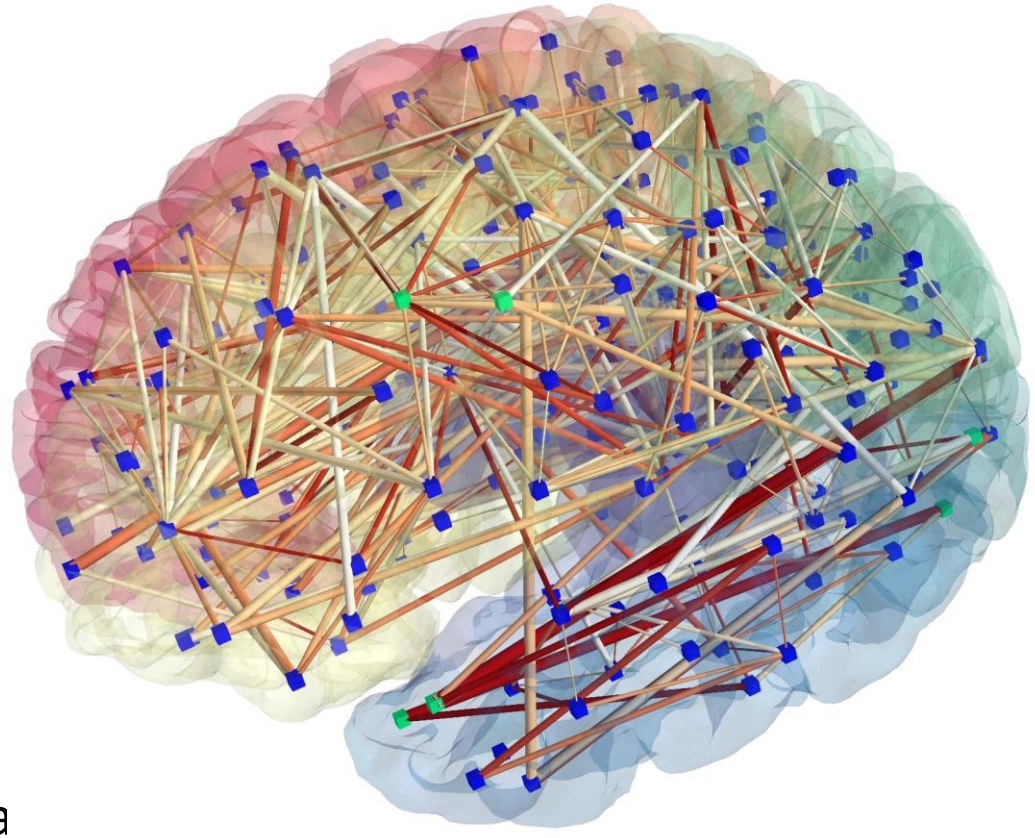
> We must recollect that all of our provisional ideas in psychology will presumably one day be based on an organic substructure.
>
> Sigmund Freud, "On Narcissism"

J Clin Psychiatry. 2014 August ; 75(8): 895–897. doi:10.4088/JCP.13l08745.

Psychiatry 3.0: All Neuropsychiatric Diseases Are Disorders of Distributed Neural Networks

"Neurological Conditions"

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



"Psychiatric Conditions"

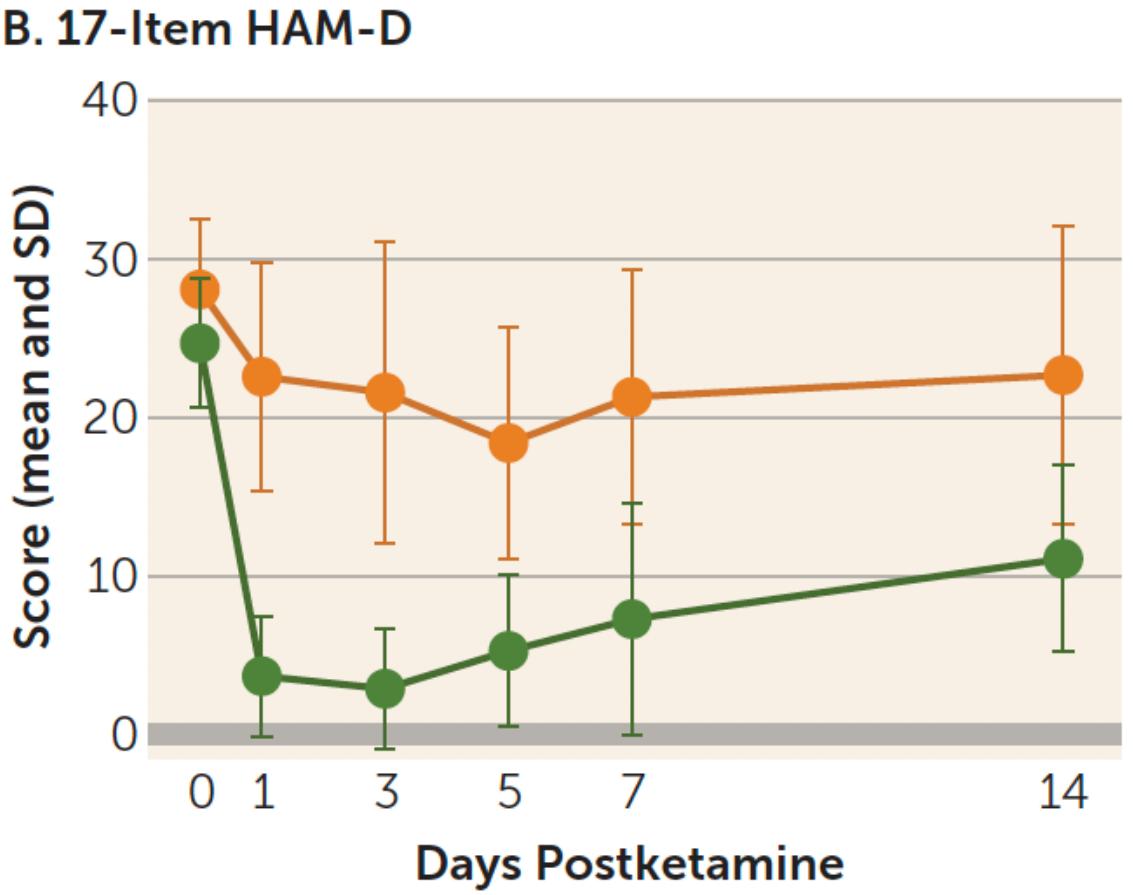
- Major Depression
- Bipolar Disorder
- Obsessive-Compulsive Disorder
- Post Traumatic Stress Disorder

Ketamine Antidepressant Efficacy

- First study of ketamine as an antidepressant demonstrated a 50% response rate (Berman 2000).
- A recent meta-analysis demonstrated response and remission rates for ketamine at 24 and 72 h, and day 7 of 52.2% and 20.6%; 47.9% and 23.8%; and 39.8% and 26.2%, respectively (Han 2016).
- A recent study demonstrate anti-suicide response rate of 55% for IV ketamine (Grunebaum 2017).
- Until recently, there have been no human studies demonstrating the mechanism of action for ketamine as an antidepressant (Williams 2016).

Naltrexone Pretreament Blocks Ketamine's Antidepressant Effect in Ketamine Responders

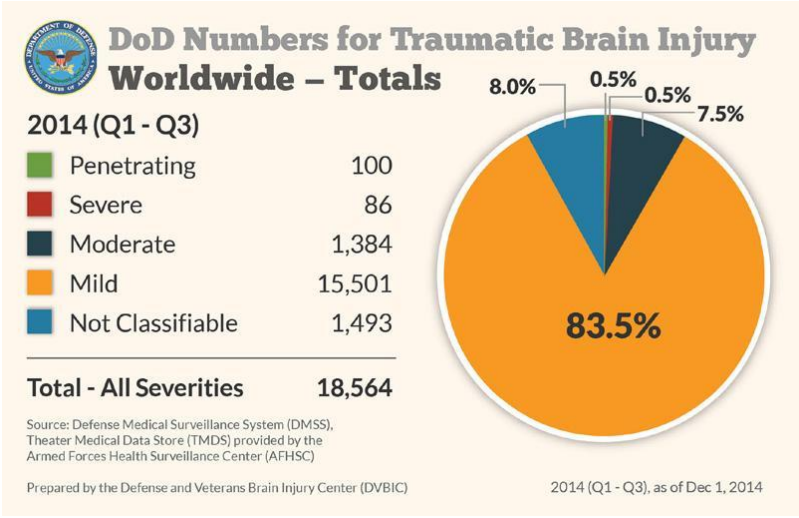
- Time course of HDRS17 scores (mean ± SEM) for patients in 2 conditions ketamine + placebo (KET+PBO) and ketamine + naltrexone (KET+NAL).
- KET+NAL scores were significantly attenuated at Day 1 and Day 3 compared to KET+PBO (p=0.0006).
- 6 of 7 patients were remitters (HDRS17≤ 7) at Day 1 with KET+PBO and 0 of 7 patients were responders at Day 1 with KET+NAL.



Williams, AJP, 2018

The Problem

- Traumatic brain injury (TBI) is the “signature injury” of Iraq and Afghanistan Conflicts. Among Veterans of these recent conflicts, almost *half* (46%) screened positive for TBI (Morissette et al., 2011).
- Special Forces are at increased risk for TBI compared to conventional military (approximately 22% higher prevalence) (Garcia et al., 2021).
- A substantial portion of those affected by TBI develop symptoms that last for months or years (Vanderploeg et al., 2007).
- TBI is highly comorbid with PTSD (33-39%) (Carlson et al., 2009). Psychosocial and functional impairments are common in both disorders.
- The rate of PTSD among Special Operations Forces is almost double compared to conventional Army (Hing et al., 2012)
- Both TBI & PTSD associated with suicidal ideation (Wisco et al., 2014)



The Problem

- Suicide in veterans is currently at the highest level in recorded history (Inoue et al., 2022)
- Veterans make up 20% of suicides in the US (Reisman, 2016).
- Special Operations Forces have the highest rates of death by suicide compared to both conventional military and general population (USSOCOM)
- Suicide rates among Special Operations forces are approximately 30% higher than the conventional military (SOAA.org/study-sof-suicides-military/)

Study Population - 30 Special Operations Veterans

- Male; Age: 33 - 58; Years of service: 17.5 (mean) ± 7 (SD)
- Average of 5 combat deployments
- All participants met criteria for Traumatic Brain Injury (TBI) diagnosis by history, as assessed by a neuropsychologist.

Baseline
(3 days pre-ibogaine)

Clinical assessment
(PTSD, depression, anxiety)

Cognitive functioning

MRI/EEG

Ibogaine treatment in supervised and supported setting

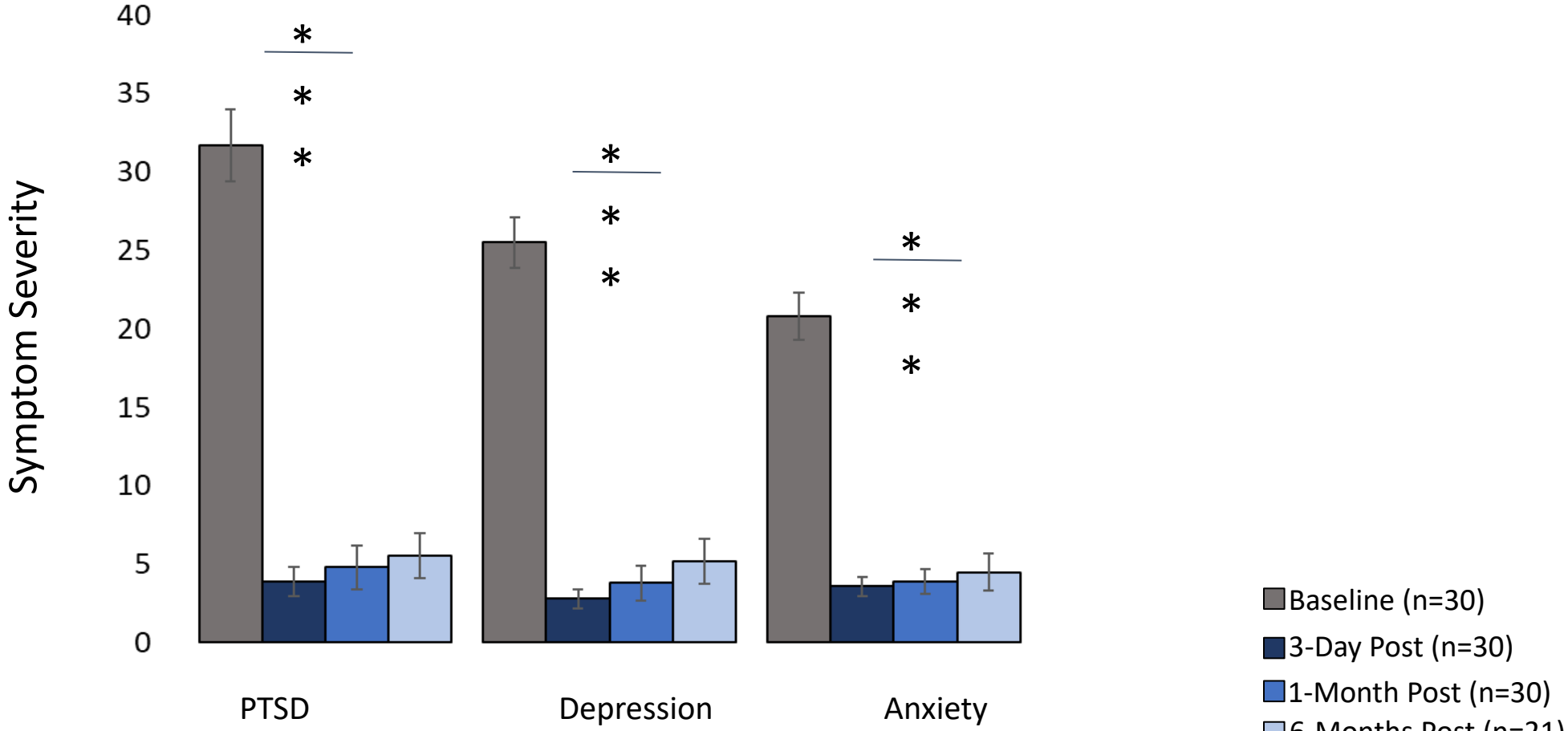
Immediate (4 days) and 1-month post

Clinical assessment
(PTSD, depression, anxiety)

Cognitive functioning

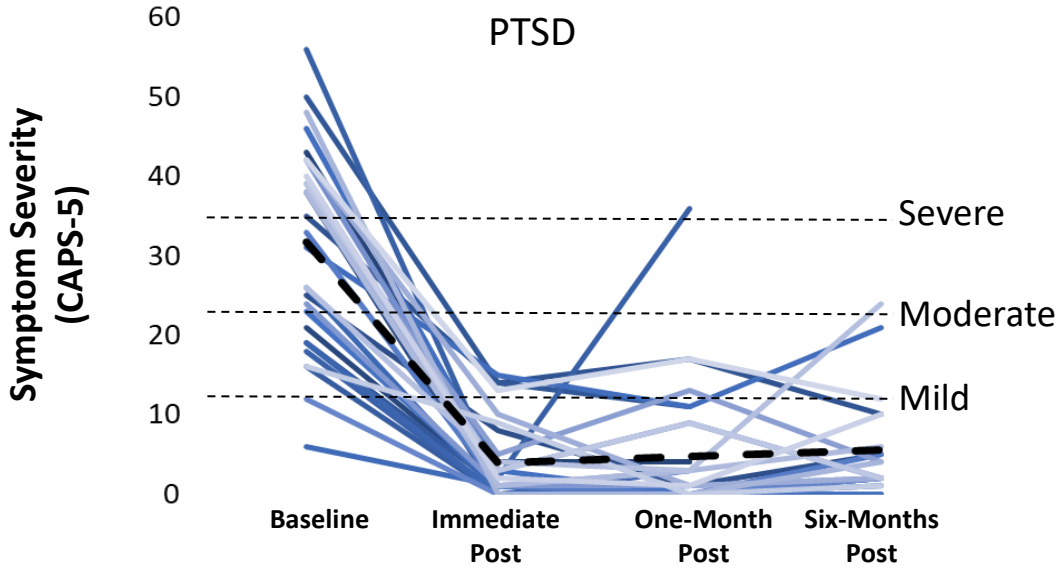
MRI/EEG

Substantial Symptom Alleviation Following Magnesium-Ibogaine



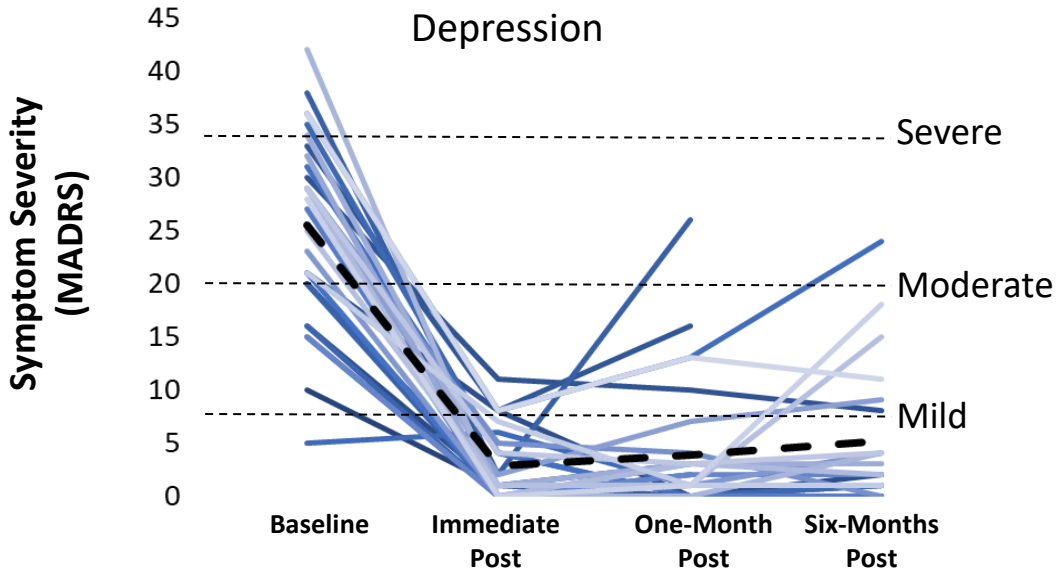
*** FDR corrected p (Baseline vs 1-Month) < 0.001; Cohen's d > 2

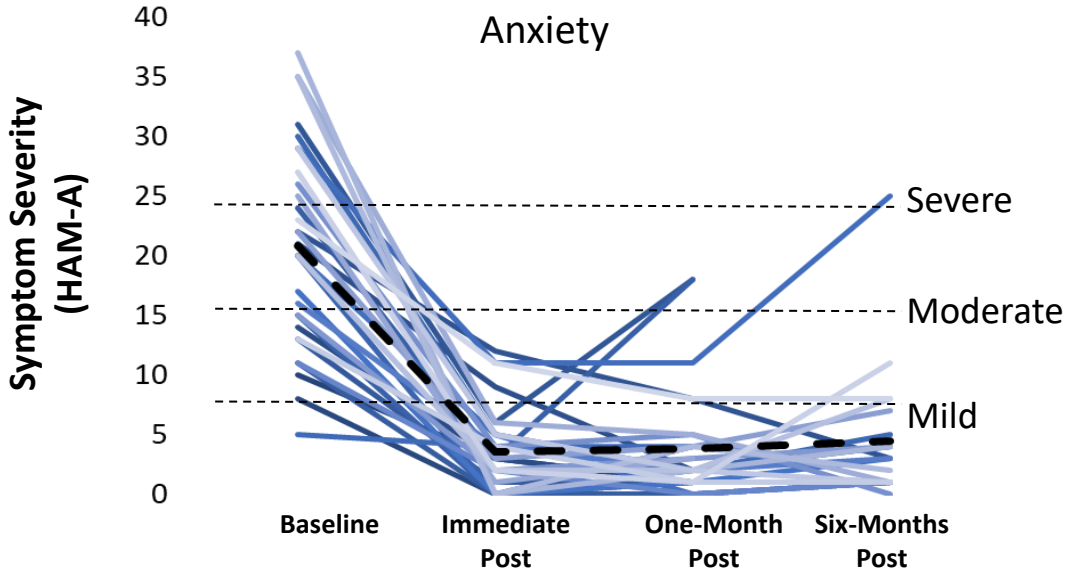
Substantial Symptom Alleviation Following Magnesium-Ibogaine



One month following magnesium-ibogaine, over 80% of veterans were within the healthy range in all three scales (PTSD, depression, anxiety).

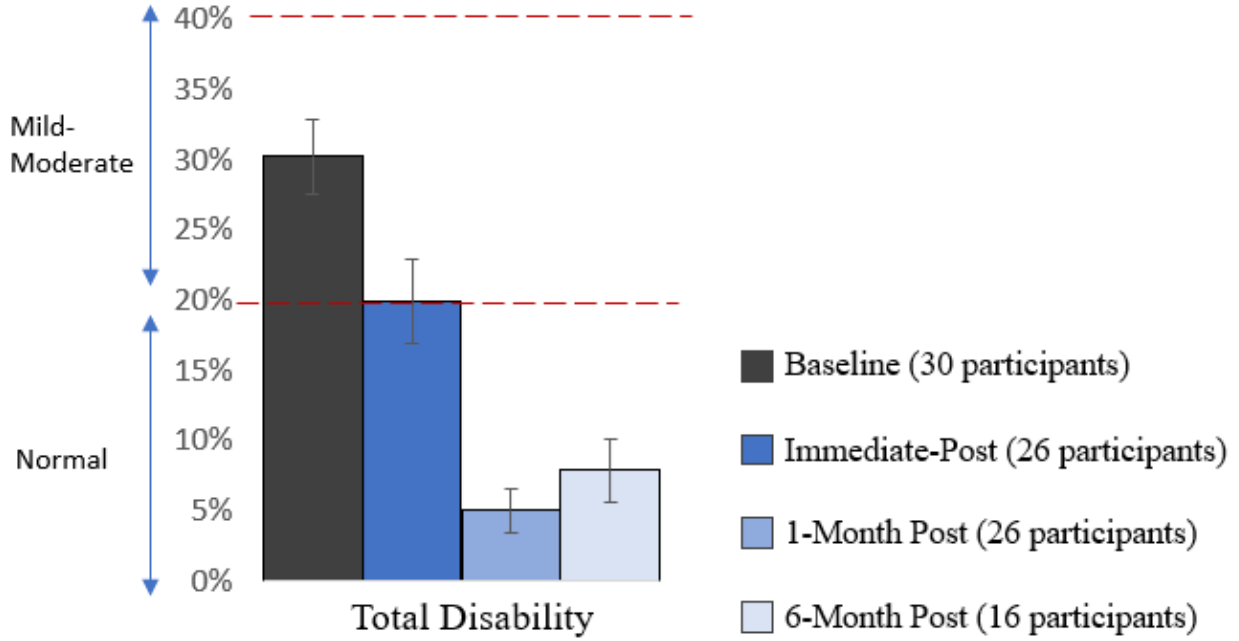
At six months follow up, over 80% were within the healthy range for PTSD and Anxiety; over 70% for depression.

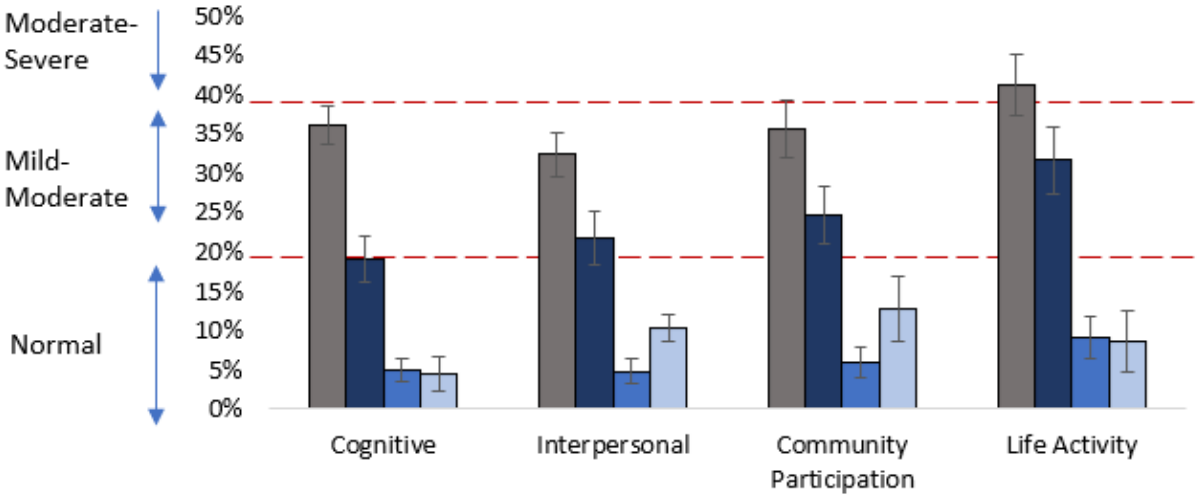




Reduced Disability Following Magnesium-Ibogaine

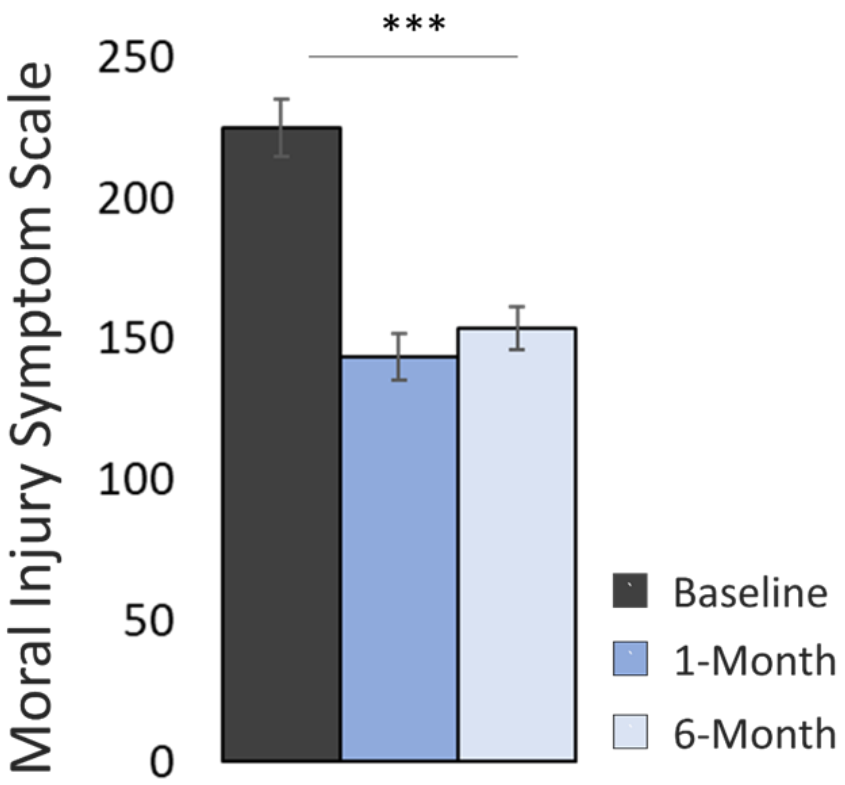
Over 90% of veterans were within the healthy range (below mild disability) at 1-month and 6-months post

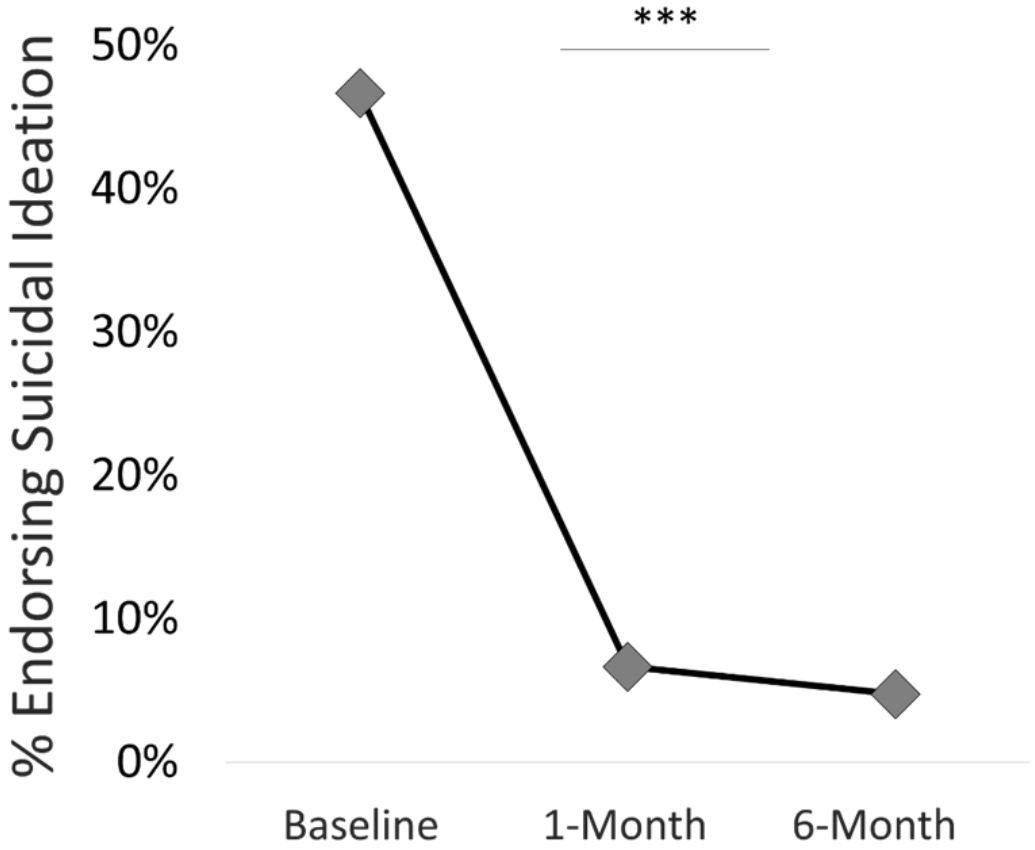




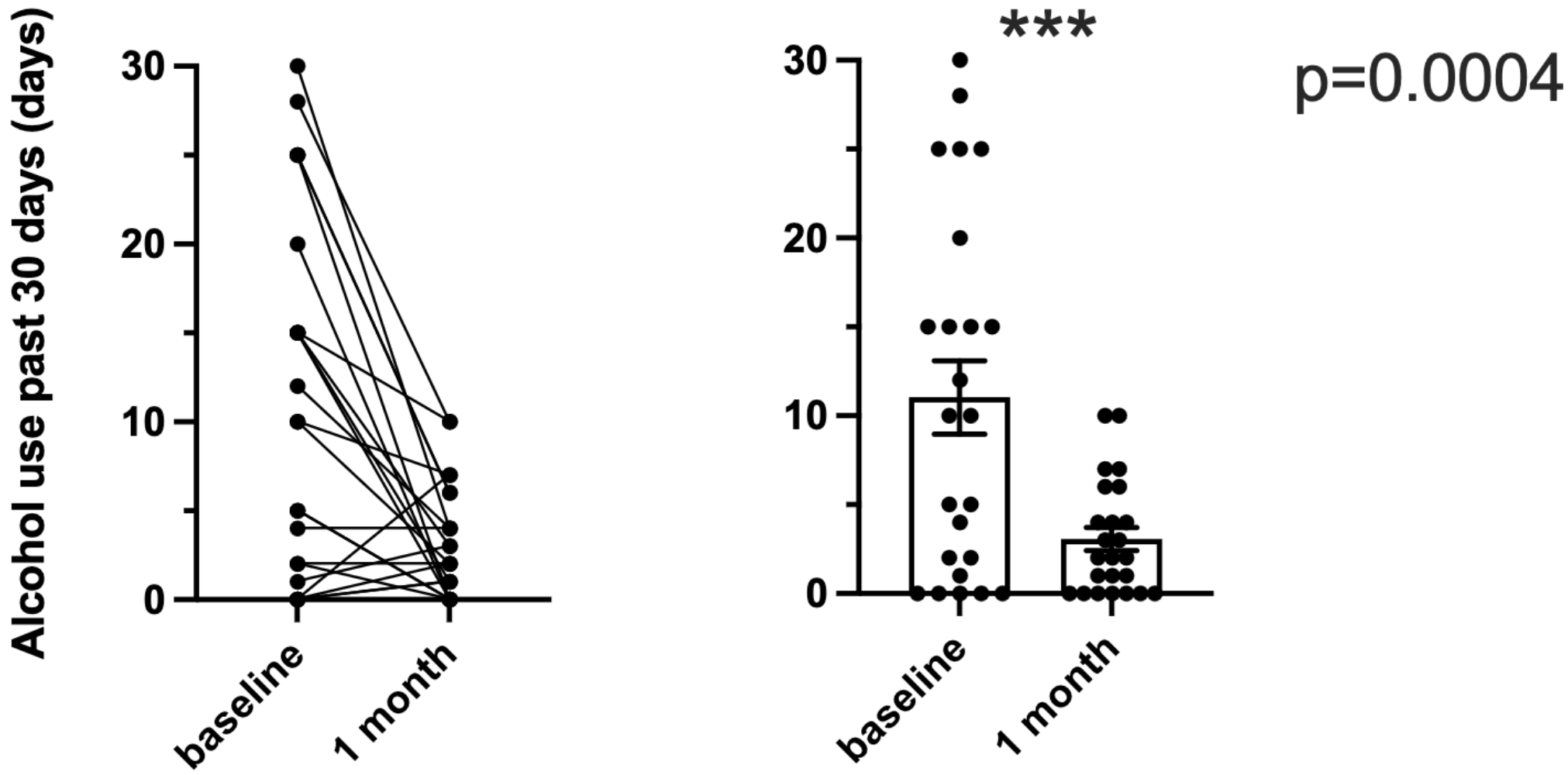
Disability was measured using the world health organization self report scale (WHODAS)

Reduced Moral Injury and Suicidal Ideation



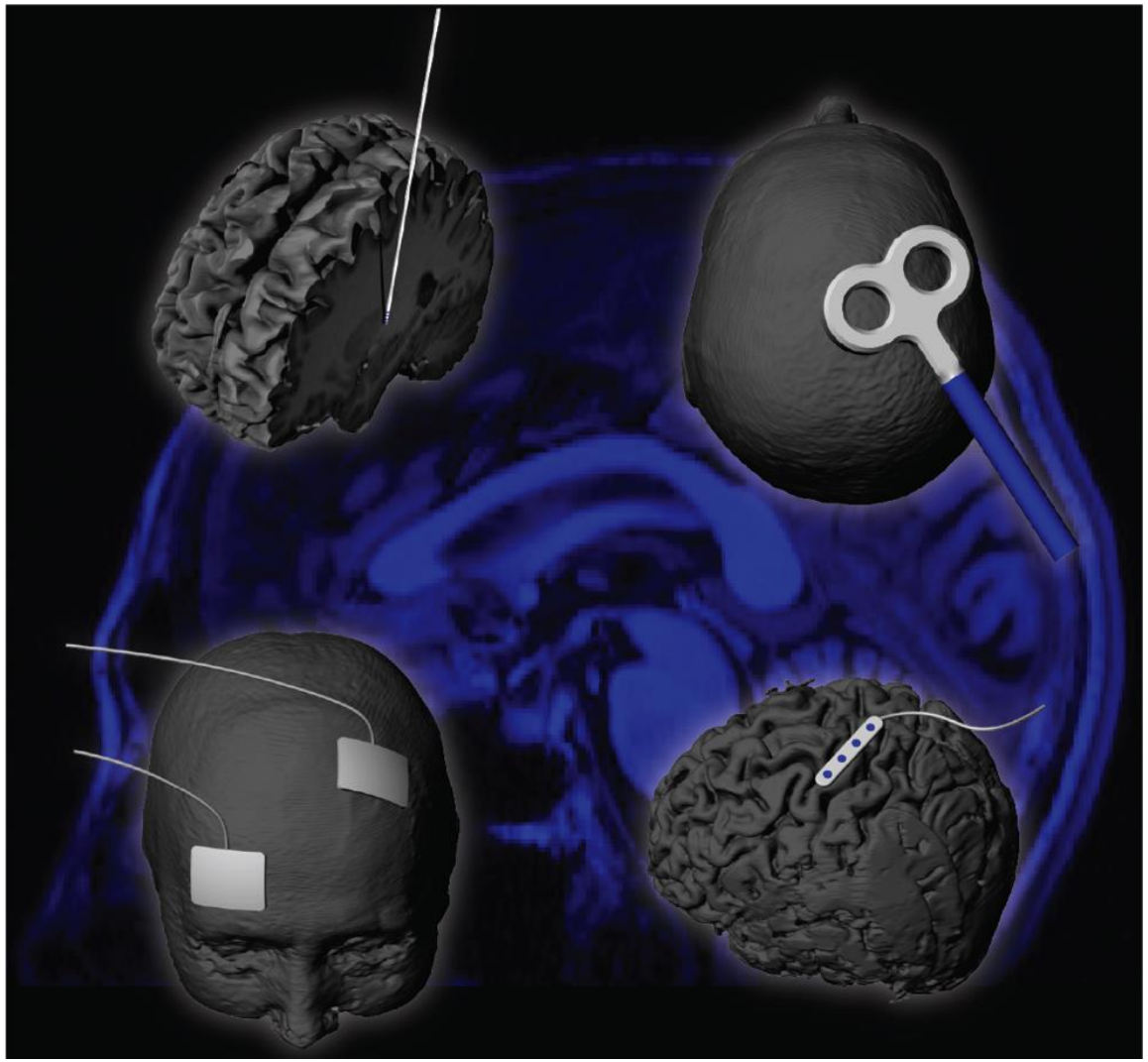


A


Alcohol use past 30 days (days)
30
20
10
0
baseline
1 month
***
30
20
10
0
baseline
1 month

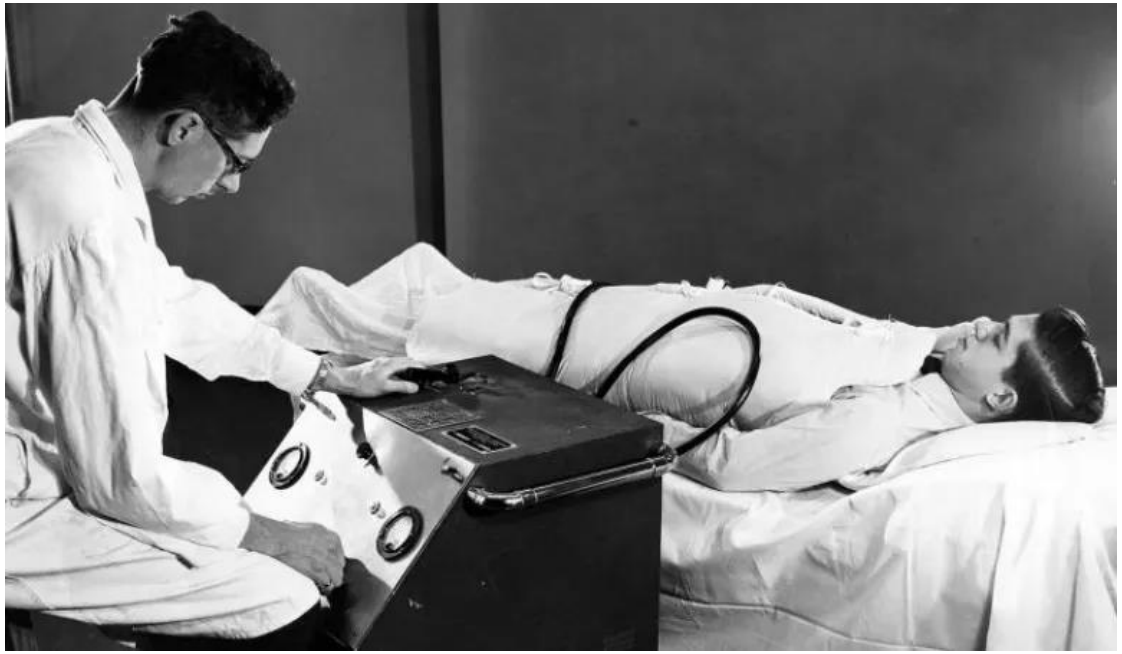
p=0.0004

Probing Psychiatric Illness



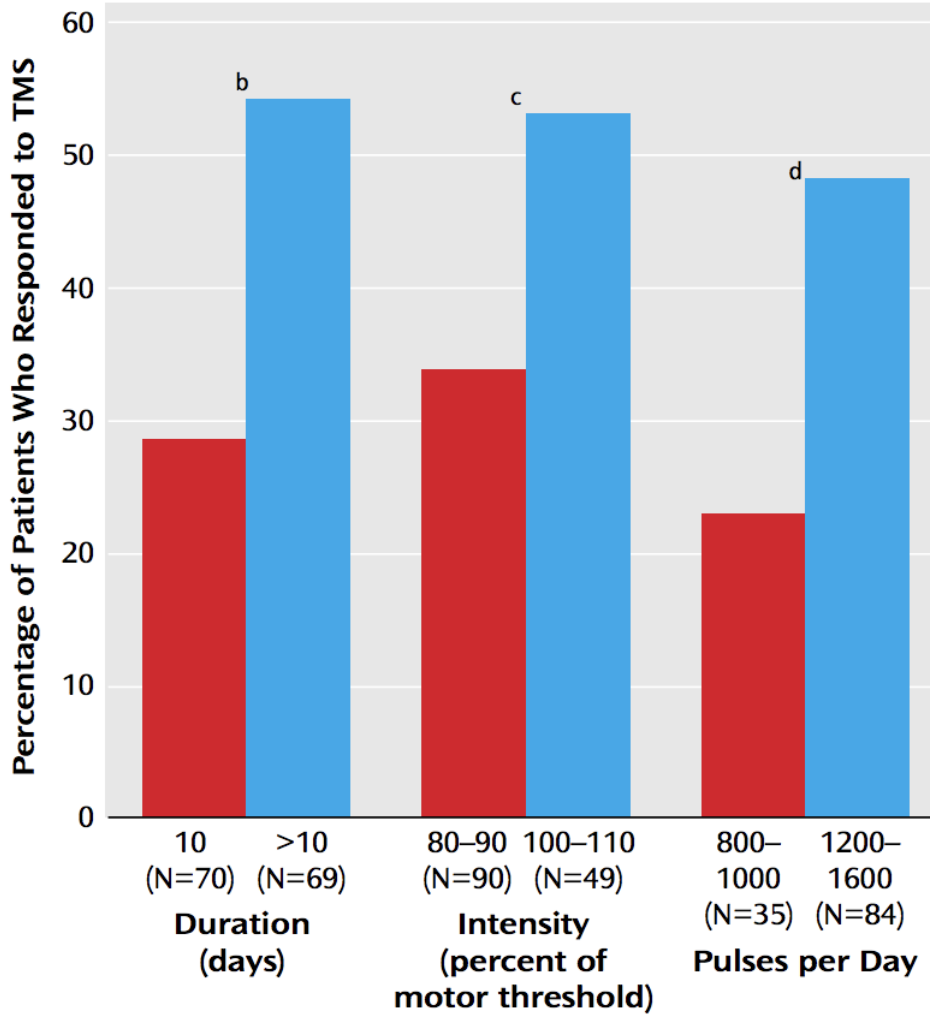
Conventional Repetitive Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation Device versus Transcutaneous Cardia Pacing Device



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

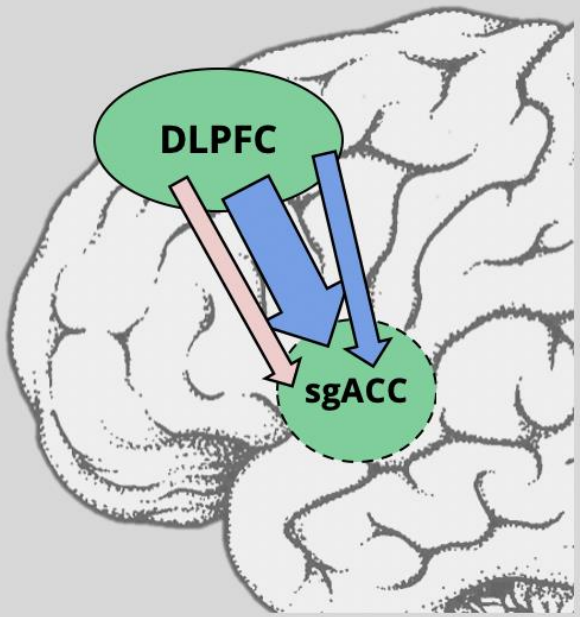
Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Mon	Mon	Mon	Mon	Mon	Mon
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Tues	Tues	Tues	Tues	Tues	Tues
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Wed	Wed	Wed	Wed	Wed	Wed
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Thurs	Thurs	Thurs	Thurs	Thurs	Thurs
rTMS	rTMS	rTMS	rTMS	rTMS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

First Generation Stimulation Parameters

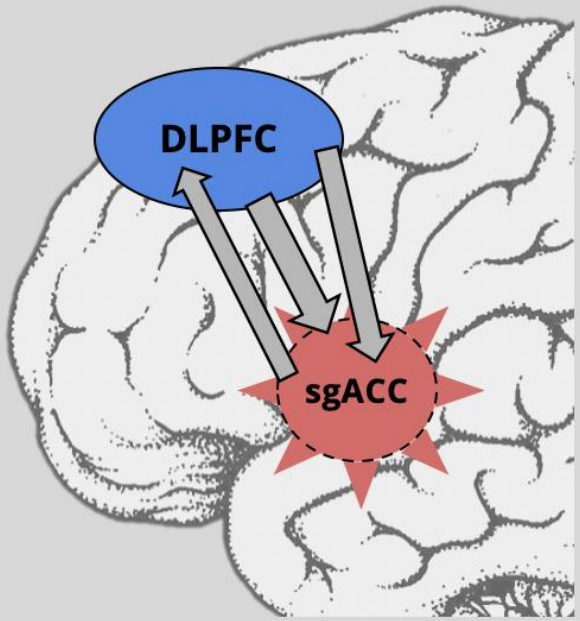
- In open label settings, ~30% remit and ~50% respond after this course.
- 62% of patient maintain response/remission at 6 mo and that increases to 84% if mTMS added in.
- Recent data suggests more pulses may increase efficacy (Yip 2017).

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

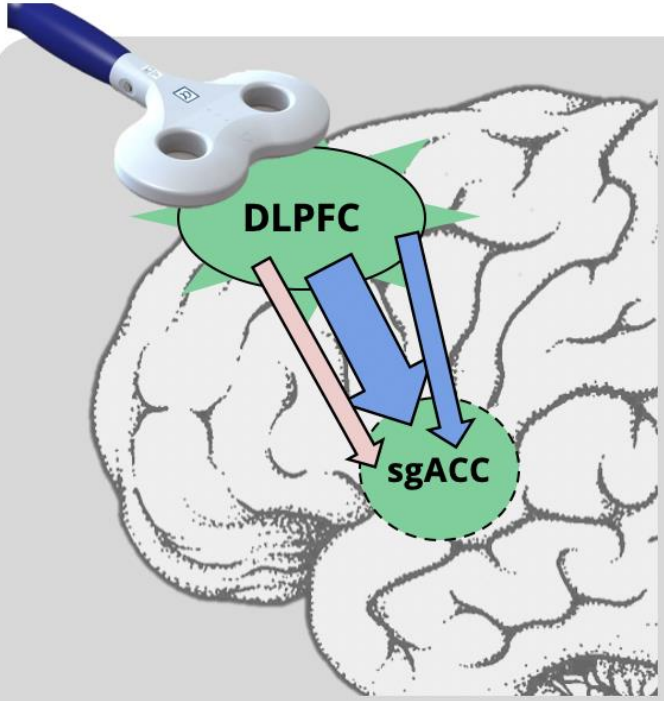
Biology of depression and TMS



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

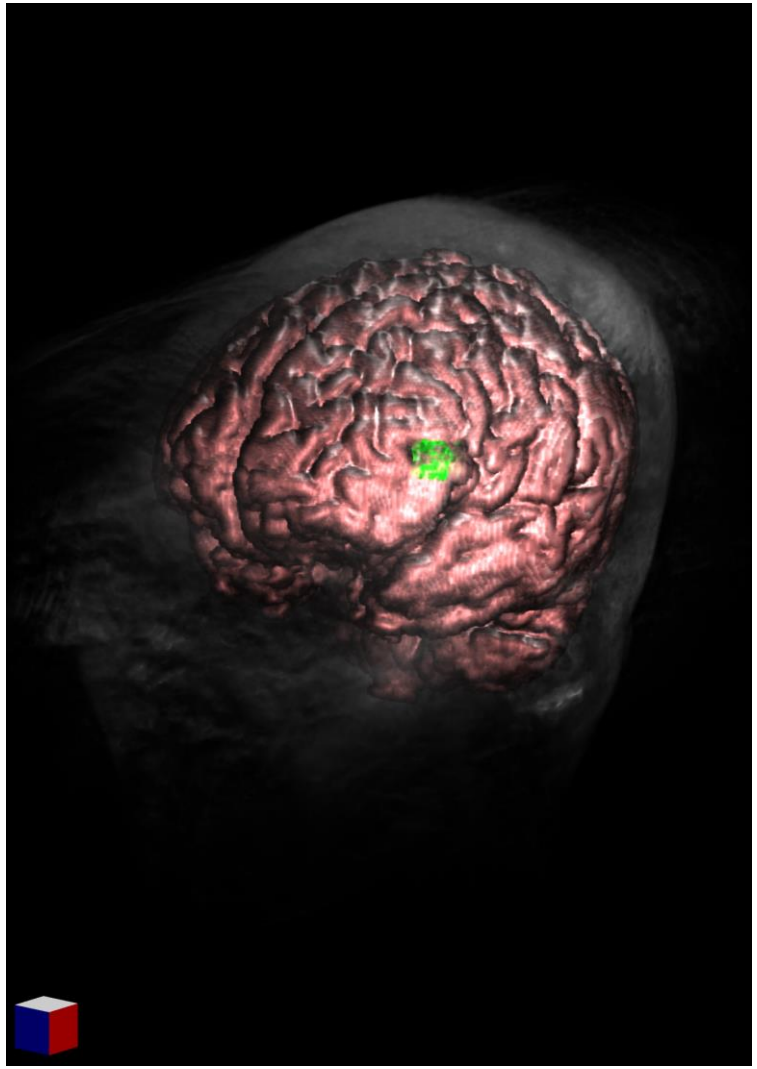


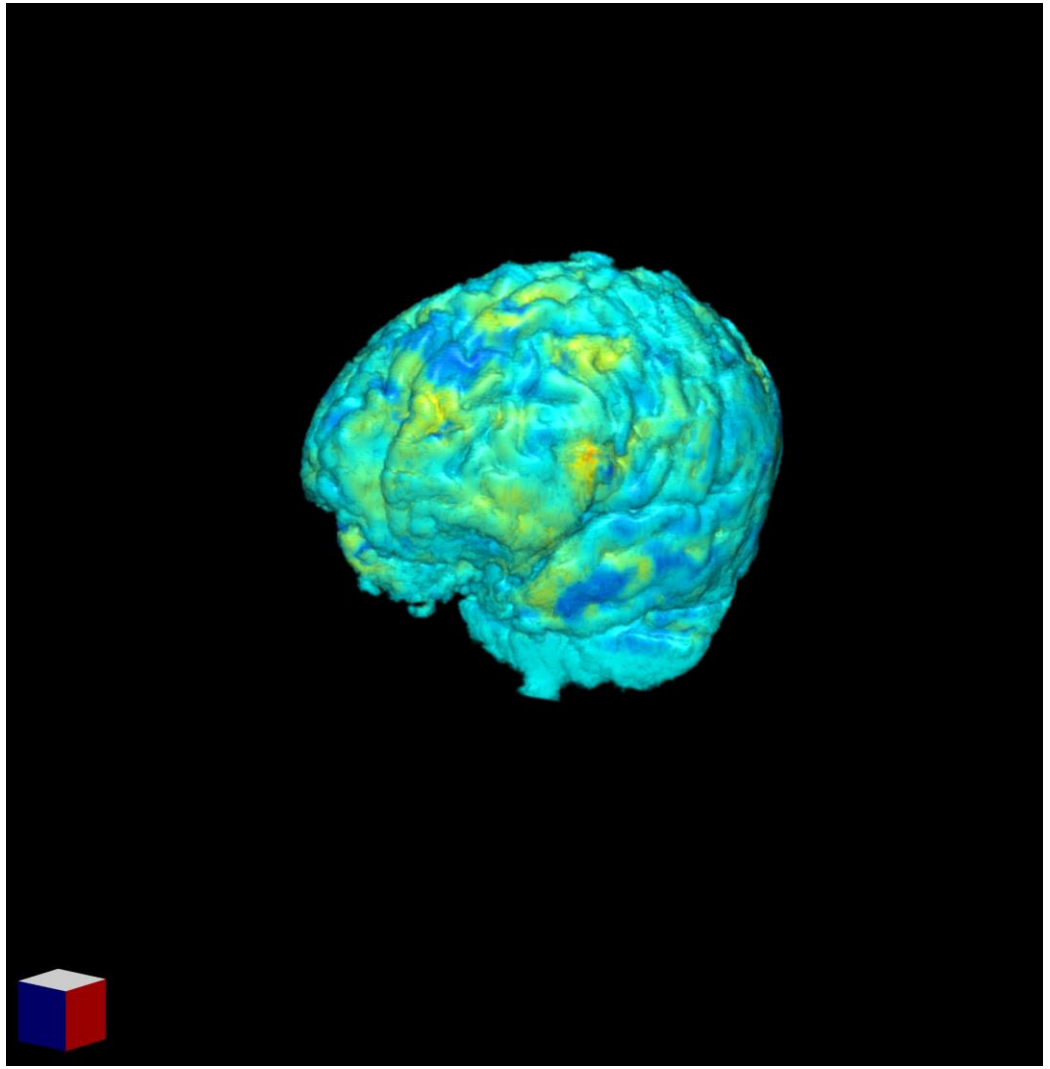
In MDD, DLPFC becomes less active and fails to inhibit sgACC. This network pathology, known for decades, causes cognitive impairment and inwardly directed negative thoughts (Baxter et al 1989, Drevets et al 1997).

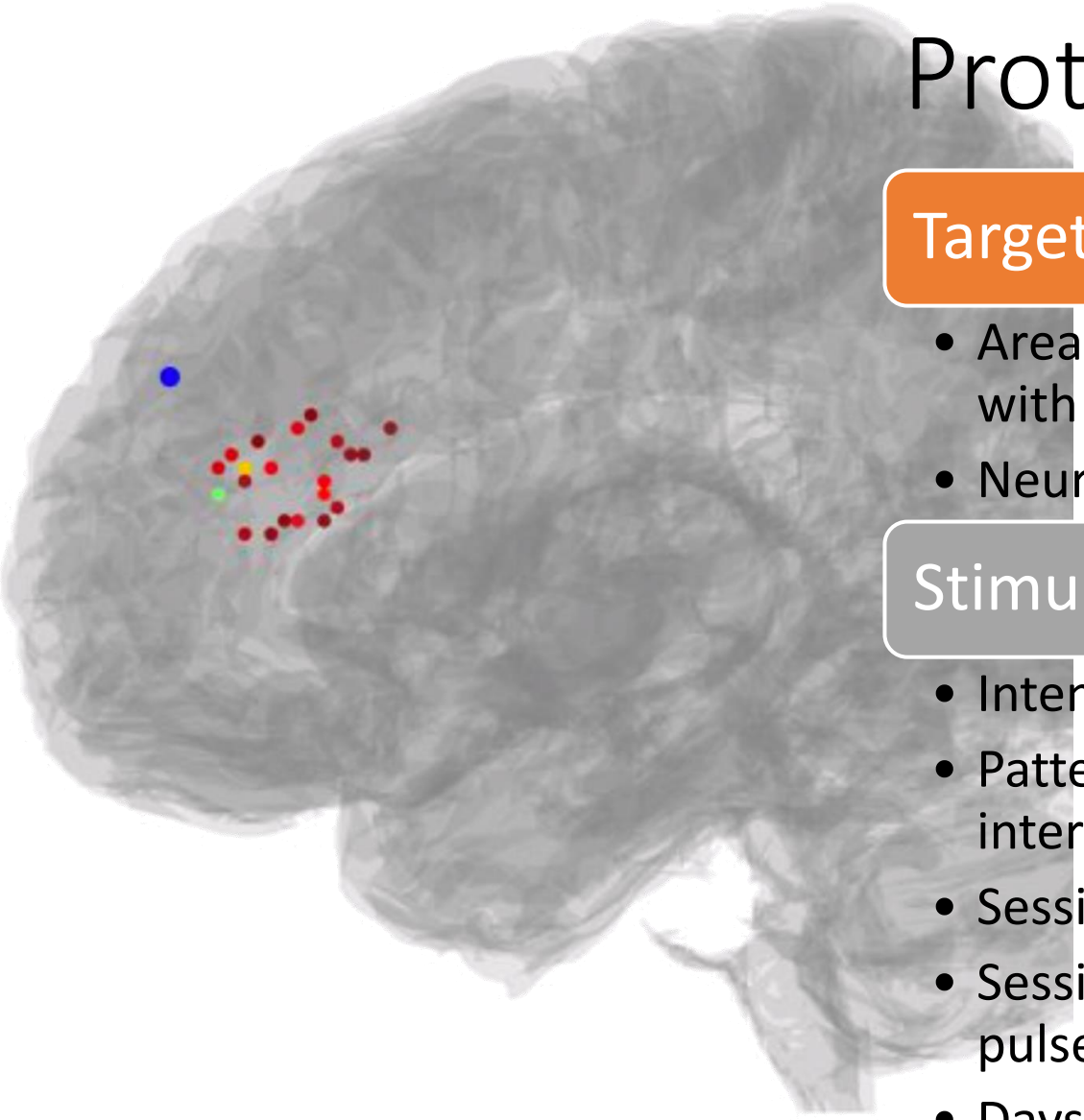


TMS stimulates DLPFC, re-activating inhibitory connections to sgACC. This corrects the network imbalance and normalizes mood regulation (Liston et al 2015; Weigand et al 2017).

Outputting Targets to Neuronavigation







Protocol

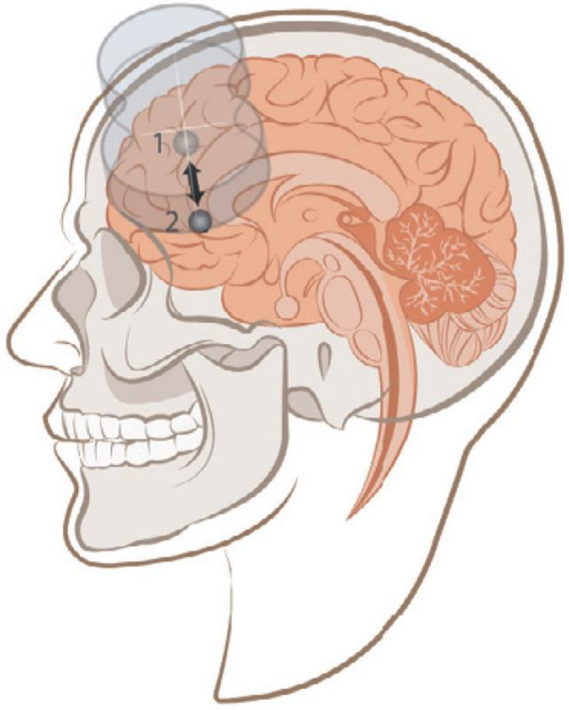
Target

- 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)

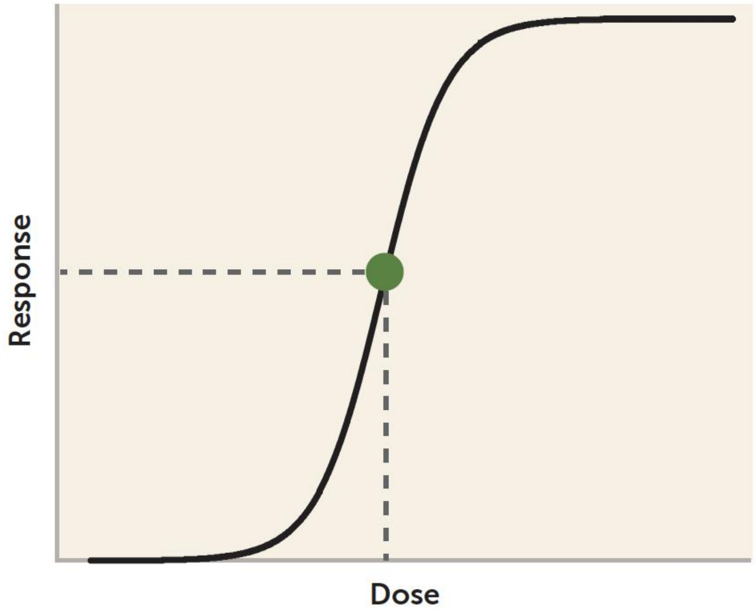
A



B

Day 1	Day 2	Day 3	Day 4	Day 5
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI

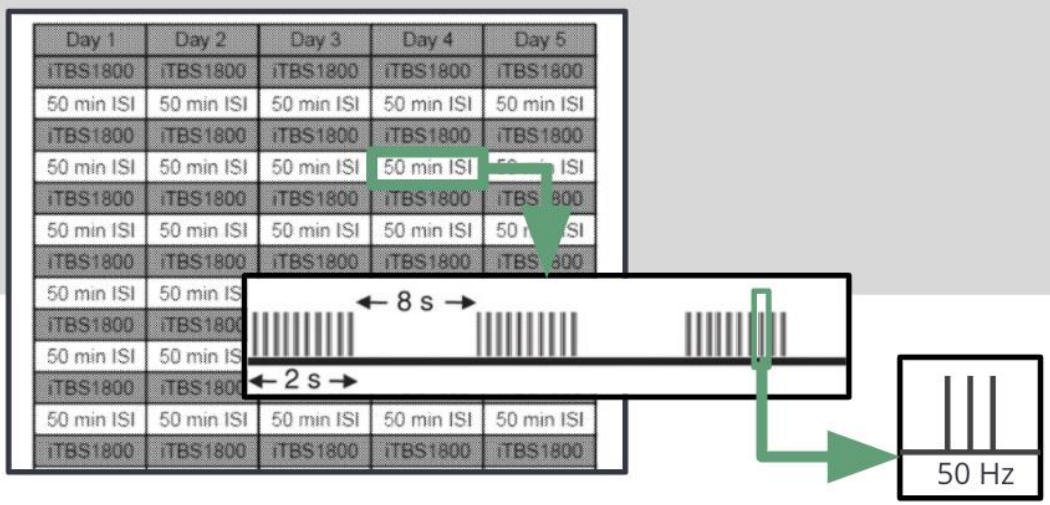
C



Patterned stimulation, personalized targets

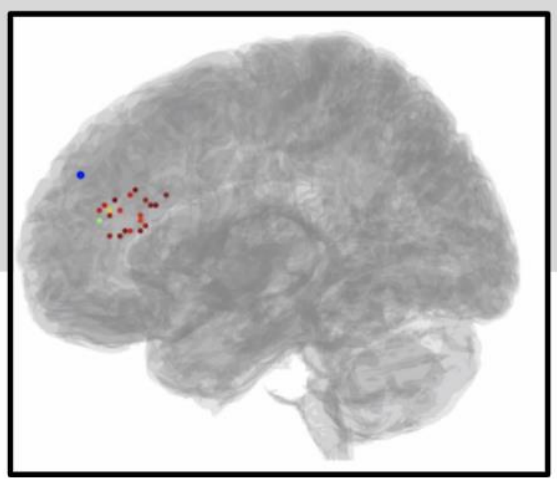
patterned dosage activates spaced learning, 60x greater potentiation of neural circuitry

- 5 days, 10 hourly sessions per day, 1800 theta-burst pulses per session
- Each day is equivalent to a conventional TMS course of treatment



SAINT proprietary algorithm identifies a personalized target to correct MDD network pathology

- Structural and functional MRI prior to treatment are input to SAINT software
- SAINT algorithm identifies optimal target



Demographics

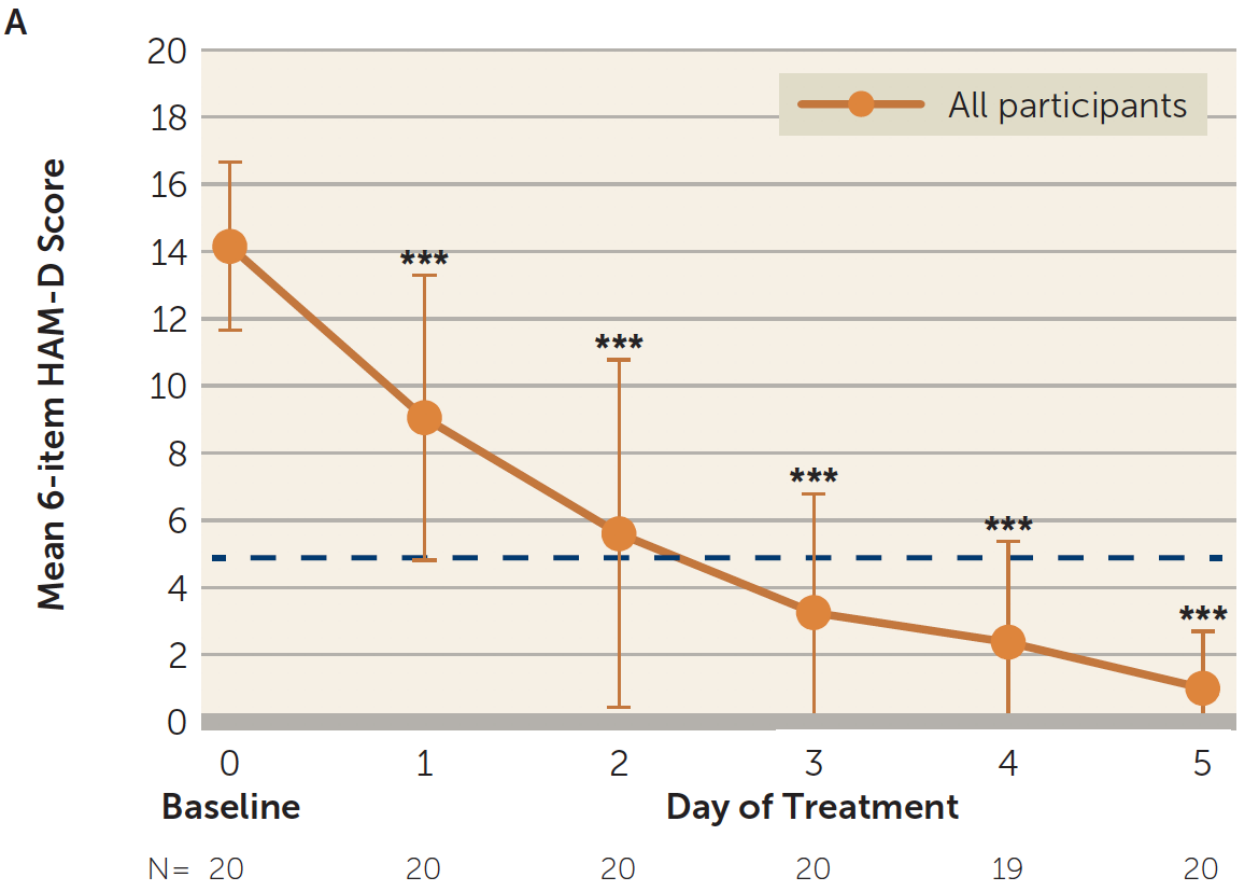
Characteristic or Measure	Mean	SD
Age (years)	44.86	17.21
Age at onset of depression (years)	21.90	13.11
Duration of depression (years)	22.95	16.30
Number of adequate antidepressant trials (lifetime)[b]	5.86	3.53
Number of adequate adjunctive medications (lifetime)[c]	1.10	0.94
Maudsley Staging Method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

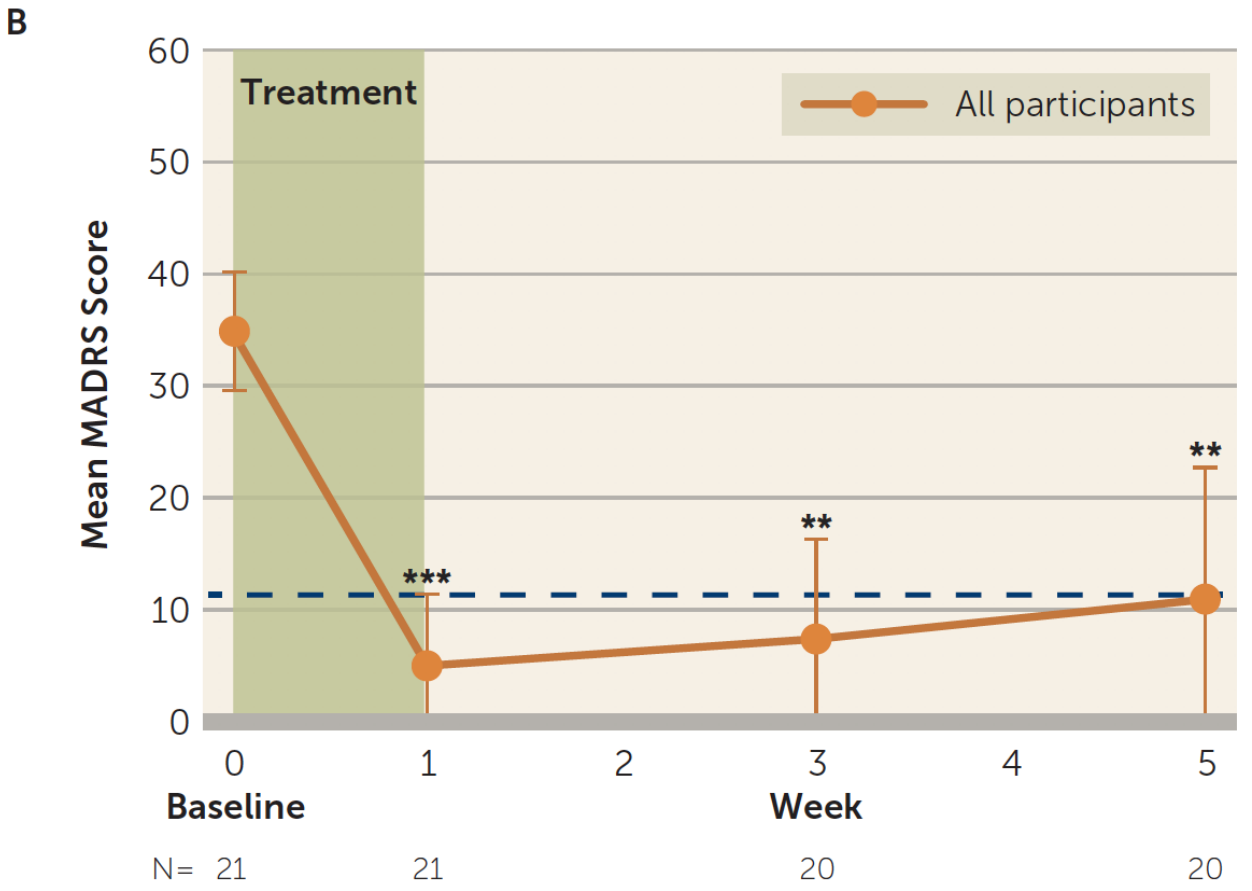
	N	%
Female	12	57.1
Participants who failed adequate medication trials[b]		
1–2 trials	2	9.5
3–4 trials	7	33.3
5–6 trials	3	14.3
7–10 trials	7	33.3
>10 trials	2	9.5
Participants who attempted FDA-approved rTMS	7[d]	33.3
Participants who attempted ECT	0	0.0

	Mean	SD
Baseline clinical measures		
MADRS	34.86	5.29
HAM-D, 17-item	25.90	4.79
HAM-D, 6-item	13.90	2.45
BDI-II (N=18)	28.78	11.68
Suicidal ideation		
C-SSRS, suicidal ideation subscale (N=19)	1.42	0.96
HAM-D, item 3	1.38	0.67
MADRS, item 10	2.38	0.80

Cole, 2020

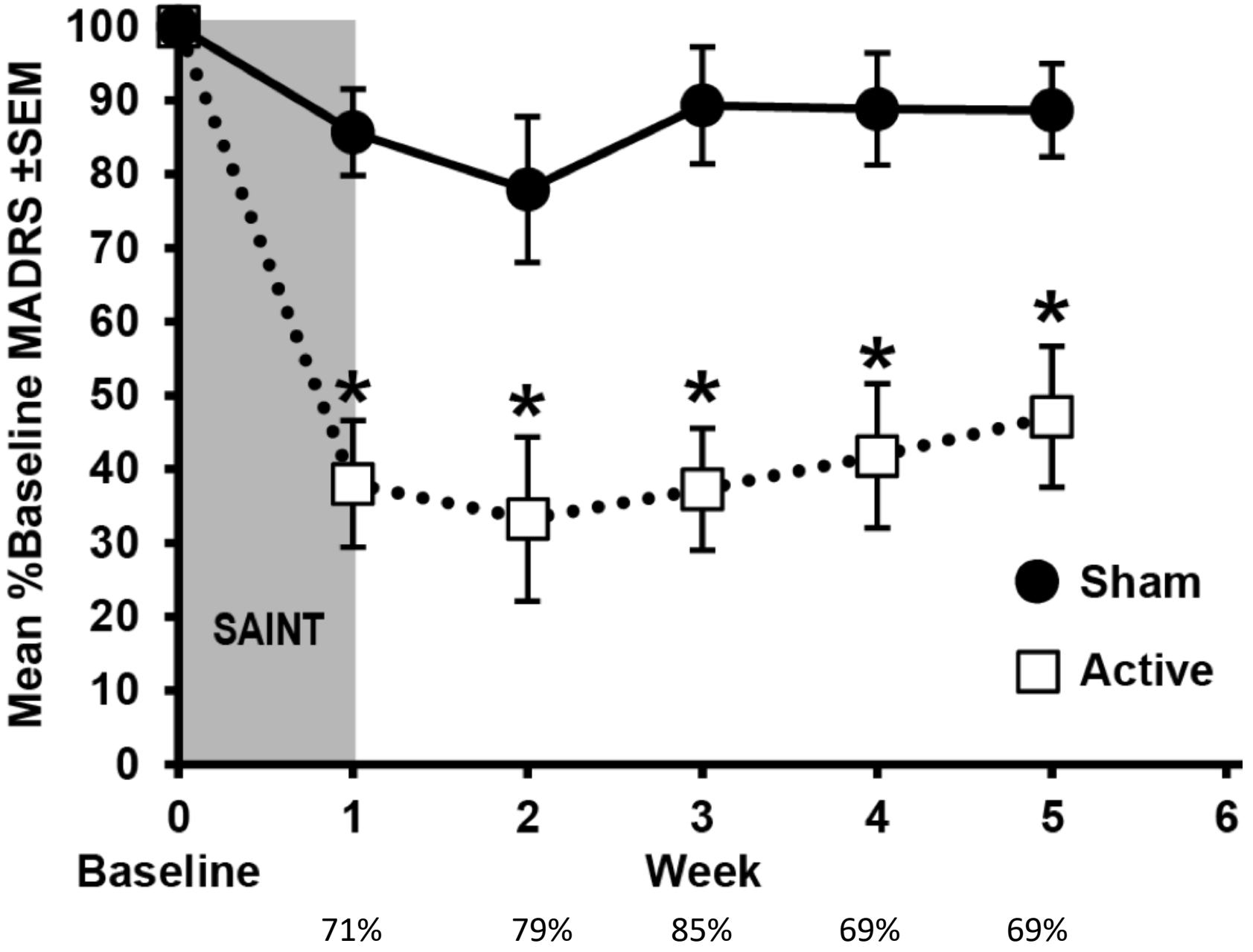
Results



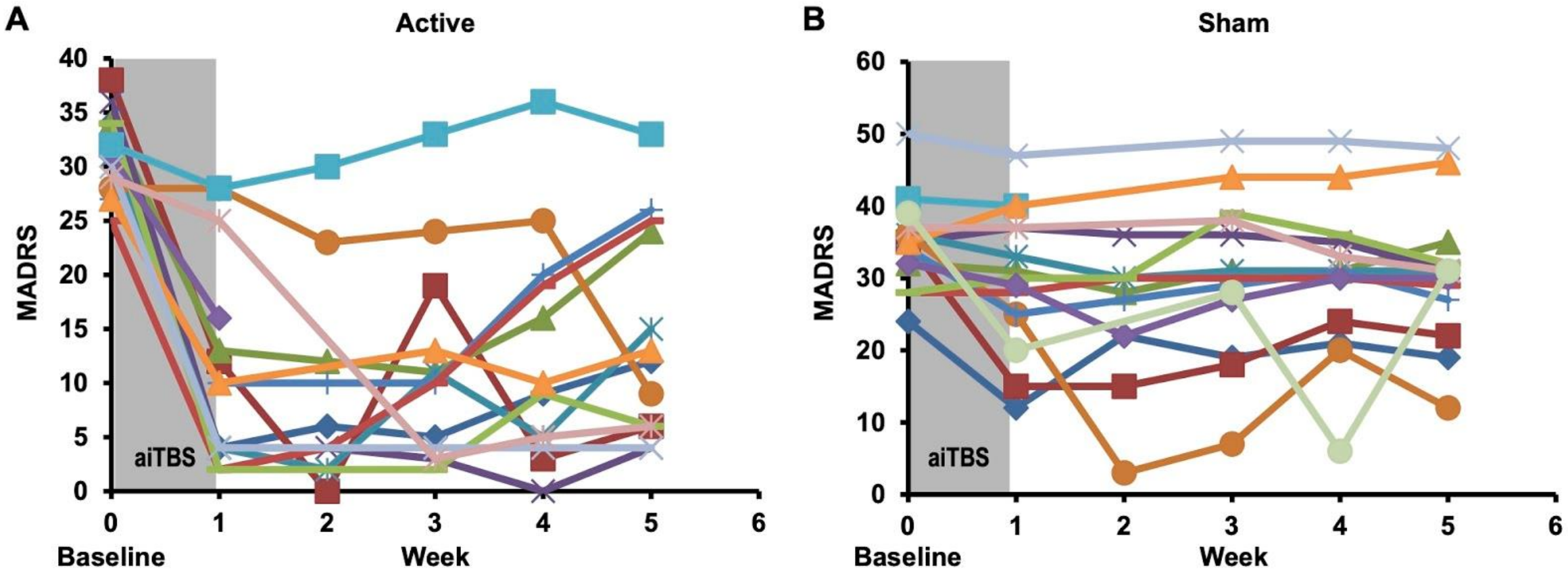


Cole, 2020

Primary Outcome



Cole AJP 2022



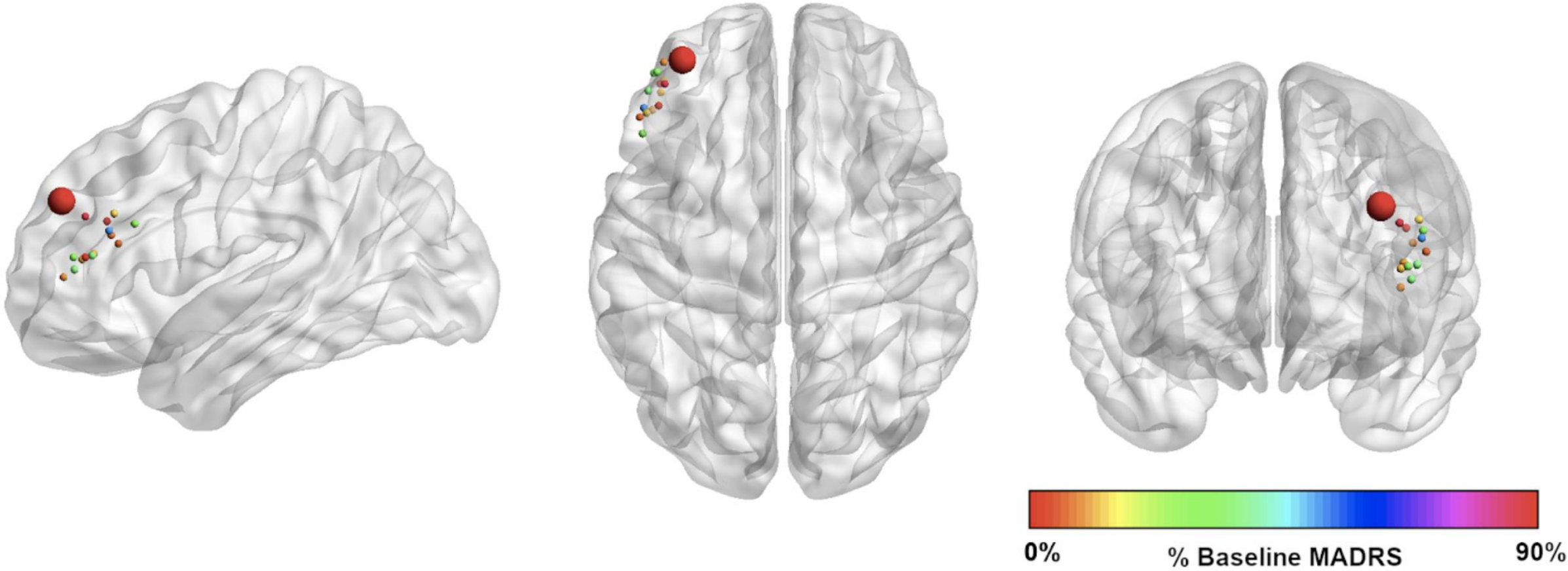
78.57%

13.33%

Cole AJP 2022

% MADRS change

a



Cole AJP 2022

FDA

BREAKTHROUGH DEVICE DESIGNATION

FDA

CLEARED

Center for Medicare & Medicaid

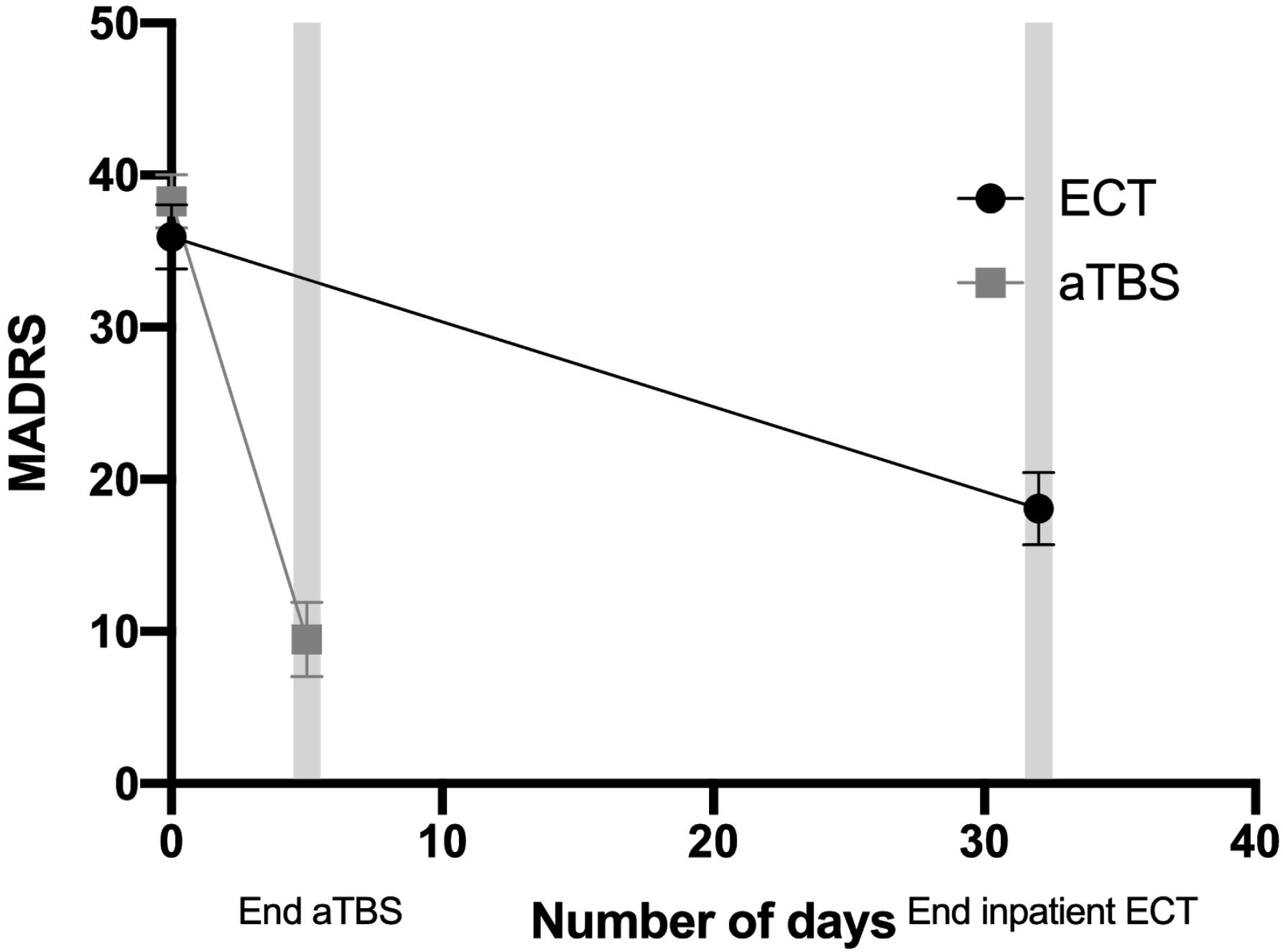
INNOVATION

Suicidal Inpatients

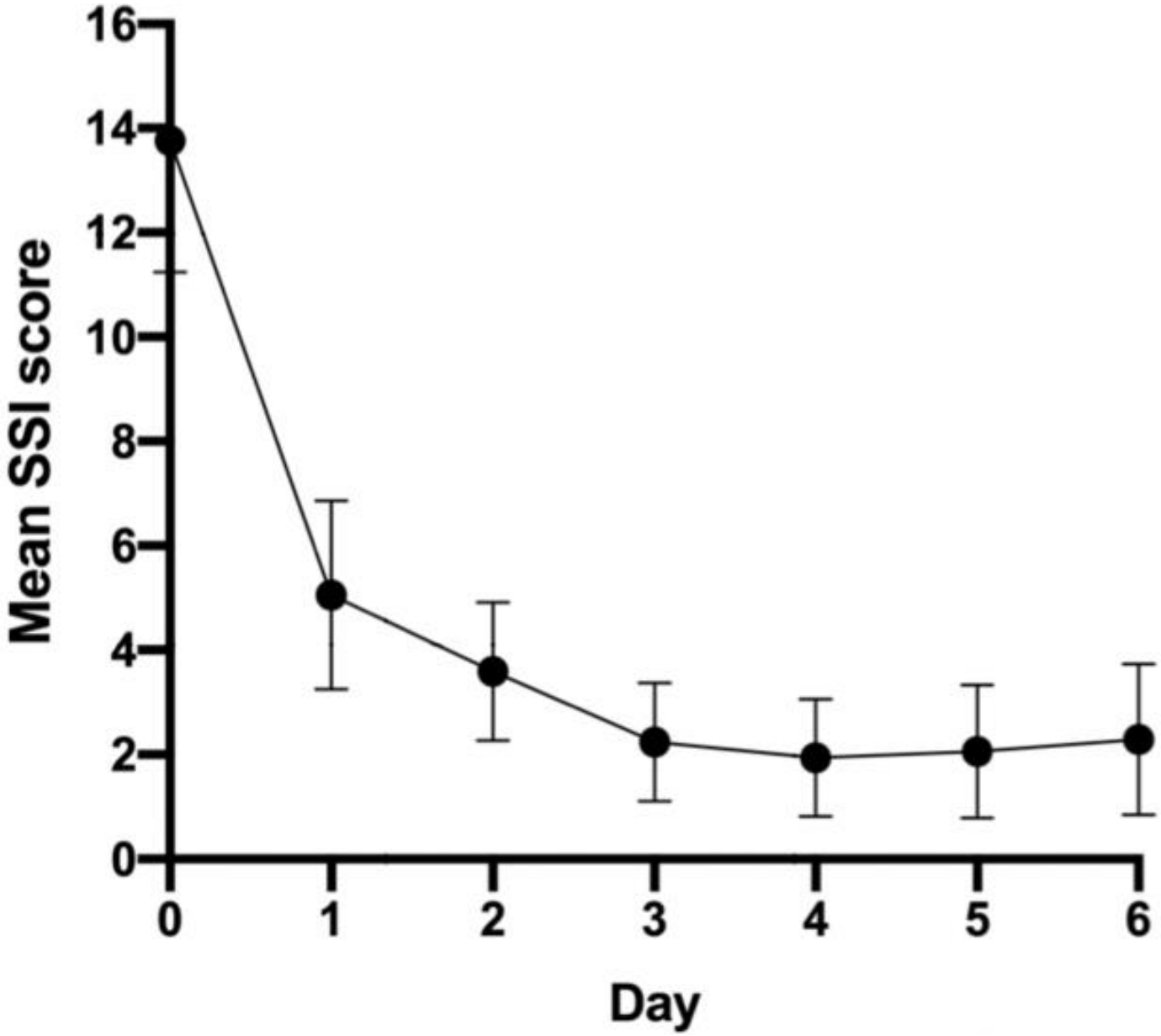
Demographics

Participant info	Mean (SD)
N	12
Gender (male:female)	10:2
Age	49.67 (16.81)
Age of onset of depression	29.22 (21.08)
Number of antidepressant failures (lifetime)	4.92 (3.37)
Number of adjunctive medications (lifetime)	0.73 (.65)
Number of participants attempted rTMS	1
Number of participants attempted ECT	3
Maudsley Staging Method Score	9.50 (2.58)
Number of previous suicide attempts	1.58 (1.38)
Number of previous hospitalizations	1.83 (1.53)

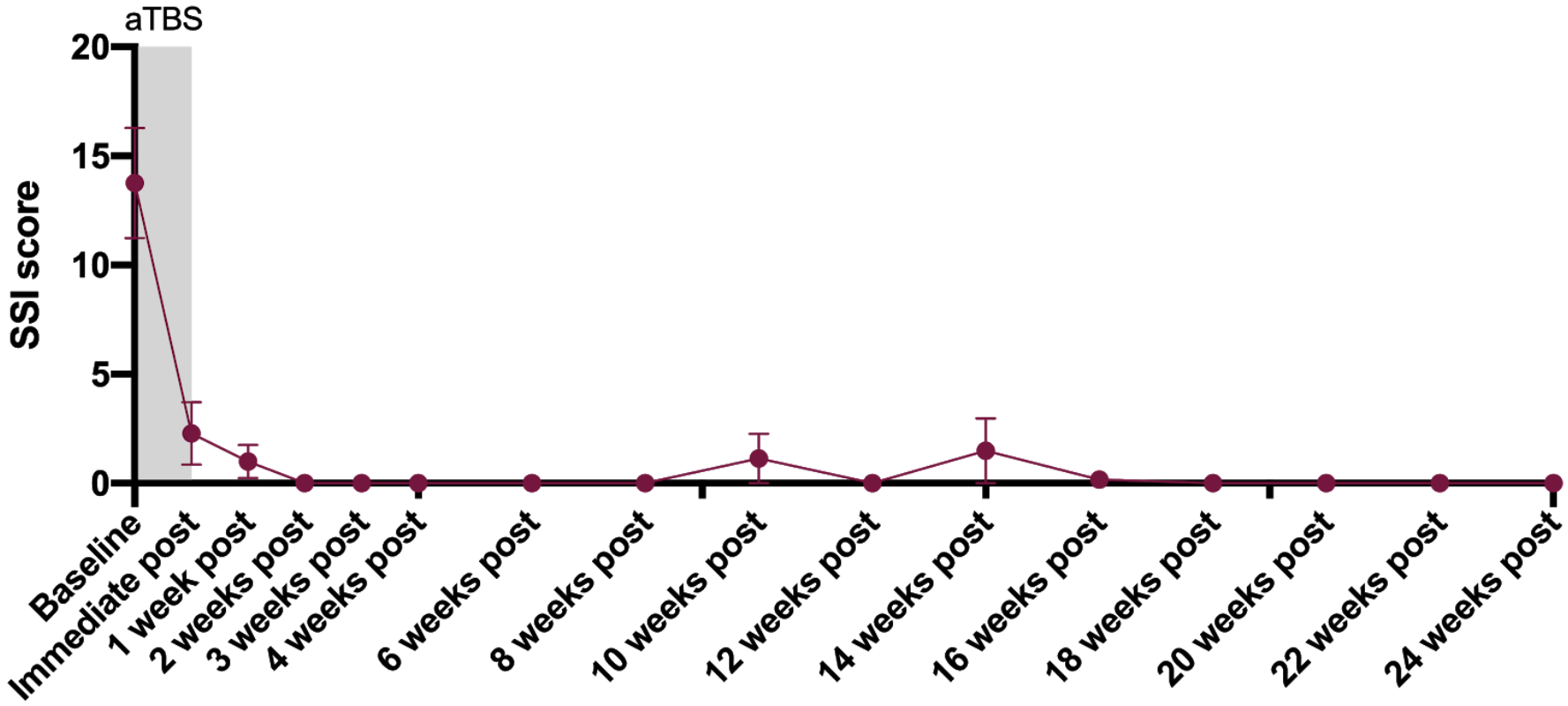
aiTBS vs ECT


MADRS
50
40
30
20
10
0
0
10
20
30
40
ECT
aTBS
End aTBS
Number of days
End inpatient ECT

Change in SI



Change in SI


aTBS
SSI score
20
15
10
5
0
Baseline
Immediate post
1 week post
2 weeks post
3 weeks post
4 weeks post
6 weeks post
8 weeks post
10 weeks post
12 weeks post
14 weeks post
16 weeks post
18 weeks post
20 weeks post
22 weeks post
24 weeks post

BSL Staff & Collaborators

Faculty

1. Nolan Williams, MD. Director.
2. Greg Salem, MD. Medical Director.
3. Ian Krater, MD. Director, Non-invasive Neuromodulation.
4. Flint Espil, PhD. Director, Psychology.
5. Mahendra (Mach) T Bhati, MD Invasive Neuromodulation.
6. Ryan Ash, MD, PhD Director, Translational Neuroscience.
7. Tom Knightly, MD, Stanford Instructor

Senior Staff

1. Nick Bassano, MSW. Administrative Manager.
2. Noriah Johnson, CRC. Head, Neuroimaging/EEG.
3. Mehdi Husain, ACRP-CP. Regulatory Specialist.
4. Irakli Kaloiani, MD. TMS treatment lead.
5. Andrew Geoly, MS. Data team lead.

Current Post-Docs/Fellows

1. Jackob Keynan, PhD. Chief Post-Doc.
2. Azeezat Azeez, PhD. Data Scientist.
3. Jennifer Lassemore, PhD. Neuroscientist.
4. Kirsten Cherian, PhD. Neuropsychologist.
5. Derrick Buchanan, PhD. Neuroscientist.
6. Igor Bandeira, MD, PhD. Clinical Researcher.
7. Mia Gholmieh, MD. Clinical Researcher.
8. John Coetzee, PhD. Neuroscientist.
9. Wiebke Struckmann, PhD, Neuroscientist.
10. Martin Tik, PhD. Engineer.
11. Afik Fearman, PhD. Clinical Psychologist.
12. Bora Kim, MD. Clinical Researcher.
13. Anish Mitra, MD, PhD. Neuroscience.
14. Chris Austelle, MD. Psychiatry Resident.
15. David Benrimoh, MD. Neuropsych Fellow.
16. Lucy Lan, MD. Interventional Fellow.

BSL Staff & Collaborators

Staff

1. Ali Hajj-Younes. Administrator.
2. Anna Chaiken, MS. Data Analyst.
3. Malvika Sridhar, MS. Data Analyst.
4. Xiaoxian Xian, PhD. Data Analyst.
5. Or Keynan, MA. Clinical Psychologist.
6. Lauren Ashley Anker, PhD. Clinical Psychologist.
7. Haroon Mulseh, MD. TMS Treater.
8. TJ Ford. TMS Treater.
9. Nabil Alnajjar, MD. TMS Treater.
10. Ahmed Shamma. CRC.
11. Bettina Gerez, CRC.
12. Brendan Wong, CRC.
13. Fareedah Lawal, CRC.
14. Quynh Pham, CRC.
15. Seigo Ninomiya, CRC.
16. Mackenzie Mattos, CRC.
17. Sandeep Dronavalli, CRC.
18. Saron Hunegnaw, CRC.

Collaborators

1. Conor Liston, MD, PhD. Cornell
2. Zafiris J. Daskalakis, MD, PhD. UCSD.
3. Jonathan Downar, MD/PhD, Toronto
4. Ziad Nahas, MD. University of Minnesota.
5. Vivek P. Buch, MD. Stanford University.
6. David Spiegel, MD. Stanford University.
7. Robert Malenka, MD/PhD. Stanford University.
8. Mark George, MD. Stanford University.
9. Lorrin Koran, MD. Stanford University.
10. Alan Schatzberg, MD. Stanford University.
11. Carolyn Rodriguez, MD/PhD, Stanford University
12. Scott Aaronson, MD
13. Raag Airan, MD/PhD, Stanford University
14. Boris Heifets, MD/PhD, Stanford University

BSL Staff & Collaborators

Past Post Docs & Fellows

1. James Bishop, PhD. Associate Medical Director, Eli Lilly & Company.
2. Romina Nejad, MS. Neuralink Clinical Team.
3. Jean-Marie Bataille, MD, PhD. Assistant Prof, Centre Hospitalier, France.
4. Eleanor Cole, MSc PhD. Clinical Scientist Magnus.
5. Brendon Bentzley, MD, PhD. CSO, Magnus.
6. Angela Phillips, PhD. Advanced Recovery Systems, LLC.
7. Ian Kratter, MD/PhD, Stanford Assistant Prof.
8. Nick Trapp, MD, Iowa University Assistant Prof.
9. Kirsten Cherian, PhD, Stanford Clinical Instructor.
10. Elizabeth Choi, PhD, UCSF Post-Doc.
11. Zui Narita, MD/PhD NIMH, NCMP Japan, Chief of Neurology & Psychiatry.
12. Sean O'sullivan, MD. UT Austin, Psychiatry Resident.

Past Staff

1. Romina Nejad, MS. Neuralink.
2. Claudia Tischler. Baylor University MD/PhD student.
3. Heer Amin. Columbia University MD student.
4. Fahim Barmak Marshall University Neurology Resident.
5. Clive Veerapal, Magnus Medical.
6. Katy Stimpson, Magnus Medical.
7. Tram Dinh, LVN LPCH.
8. Mike Feyder, Magnus Medical.
9. Nicole Odenwald, Stanford Center for Clinical Research.
10. Sorab Sami, Stanford Center for Clinical Research.
11. Naushaba Khan.

The BSL People

6 Faculty Members

13 Post-Doctoral Fellows

24 Staff Employees

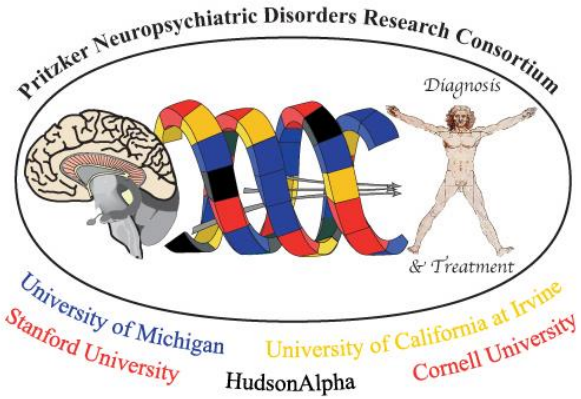
3 Clinical Trainees

14 Countries

15 Expertise

12 Active Studies

1 Goal: Find Relief


Pritzker Neuropsychiatric Disorders Research Consortium
Diagnosis
& Treatment
University of Michigan
Stanford University
University of California at Irvine
Cornell University
HudsonAlpha


NIH
National Institute
of Mental Health


ONE MIND™


NIH
National Institute of
Neurological Disorders
and Stroke


FFOR
FOUNDATION FOR
OCD RESEARCH


NIH
National Center for
Complementary and
Integrative Health


BRAIN &
BEHAVIOR
RESEARCH FOUNDATION
Awarding NARSAD Grants

Funding

Interested in a post doc?

- Email: nolanw@stanford.edu