

Expanding Access to Brain Stimulation Therapies for Serious Mental Illness

Joseph J. Taylor, MD, PhD

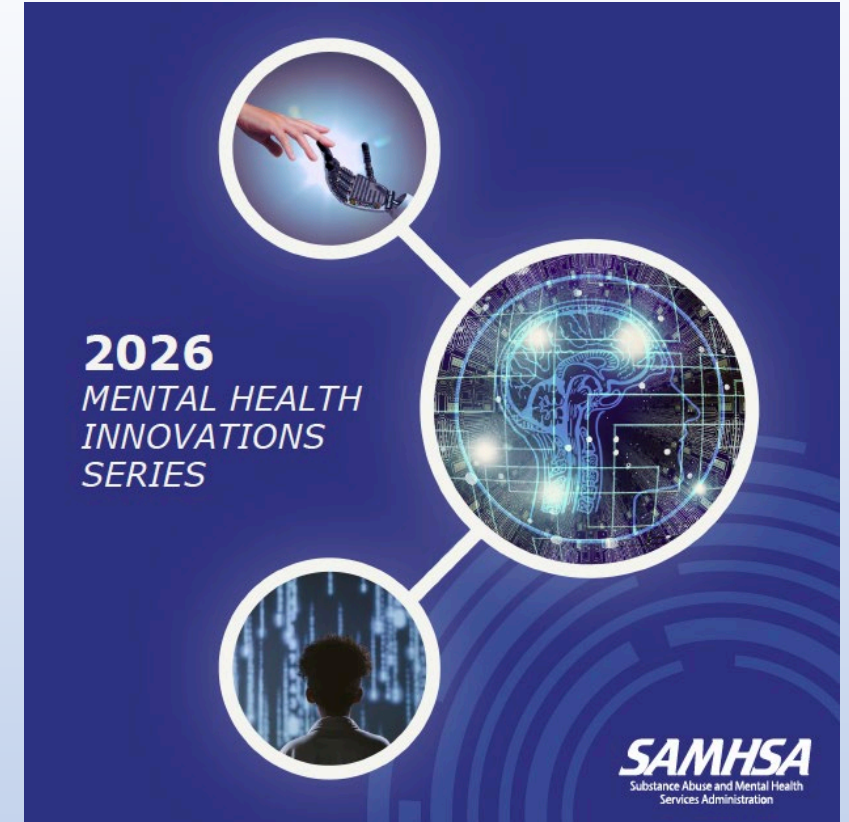
Medical Director of TMS and Director of Clinical Trials, Brigham and Women's Hospital Center for Brain Circuit Therapeutics

Debra A. Pinals, MD

Editor-in-Chief, Senior Forensic & Medical Advisor, NASMHPD

Discussants:

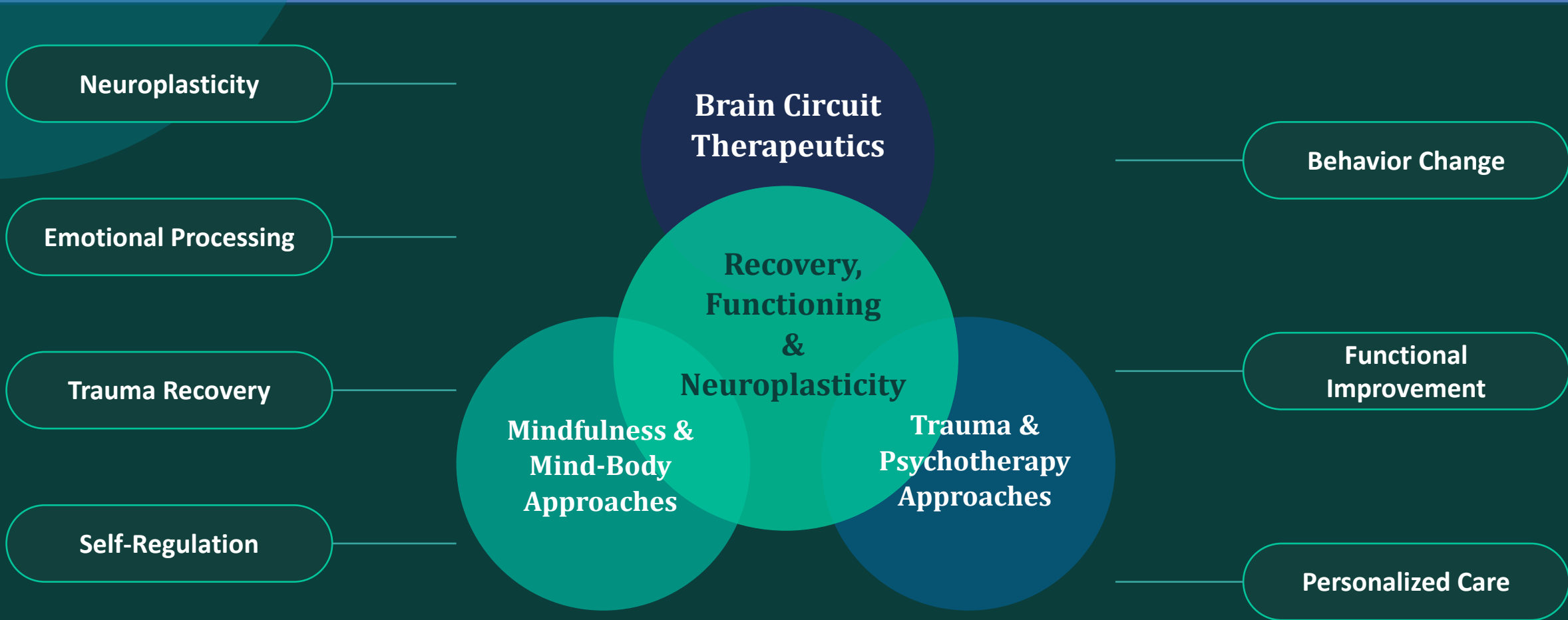
Robert Eilers, MD



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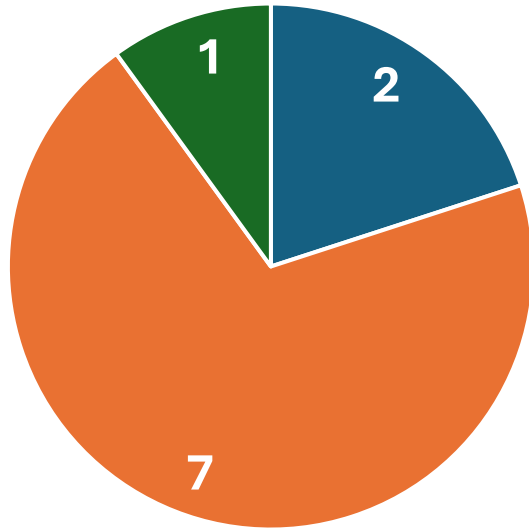
This work was developed under Task 2.2 of NASMHPD's Technical Assistance Coalition contract/task order, HHSS283201200021I/HHS28342003T and funded by the Center for Mental Health Services/Substance Abuse and Mental Health Services Administration of the Department of Health and Human Services through the National Association of State Mental Health Program Directors.

Non-pharmacological Interventions



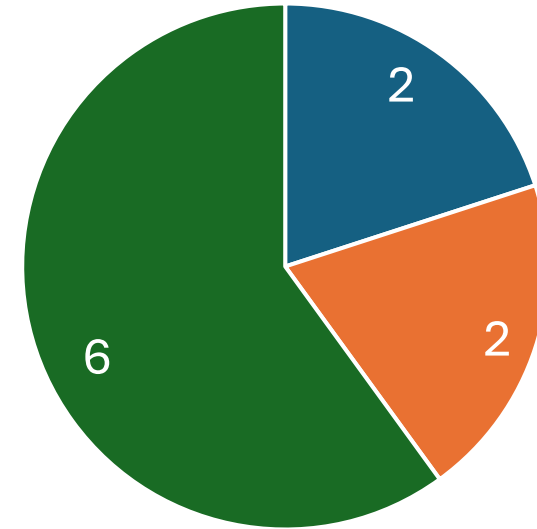
ECT & TMS Availability in State Hospitals

Availability of ECT in State Facilities



- Yes, in state hospital
- Yes, transfer to community hospital
- No

Availability of TMS in State Facilities



- Yes, in state hospital
- Yes, transfer to community hospital
- No

Brain Circuit Therapeutics

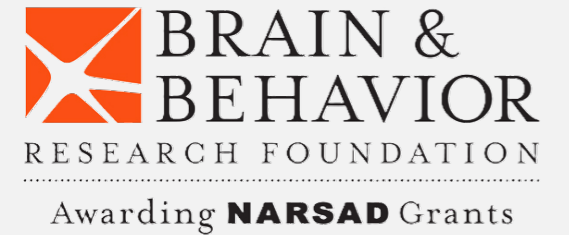
Joseph J. Taylor, MD, PhD



Funding, Disclosures, and Acknowledgements

Before we begin

Funding



Disclosures

Industry

- No salary or equity
- Planned in-kind device support from Neuronetics for investigator-initiated trial

Intellectual Property

- Provisional patent on circuit-guided TMS
- No income



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Shan H. Siddiqi, MD



Nathan Praschan, MD, MPH



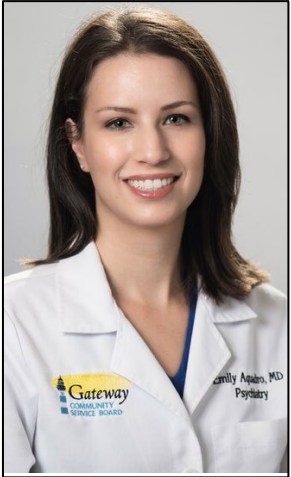
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Irene Gonsalvez, MD



Sheena Baratono, MD, PhD



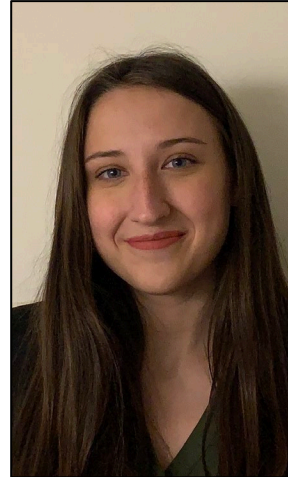
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Anjali Chandra, MD



Nicole Chiulli, BA



Dania Haj-Darwish, BA



Natalie Hall, BS



Madeleine Johnson, BS



Marina Kare, BS



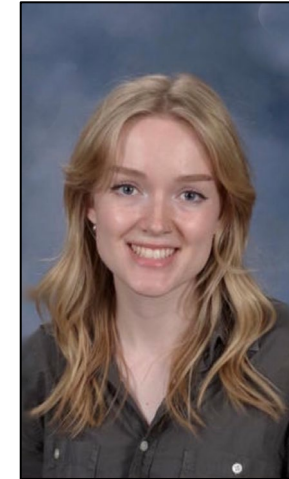
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David Lawson, BA



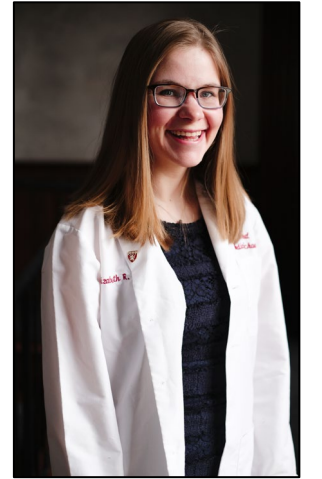
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Elizabeth Steuber, MD



Introduction

Interventional psychiatry and brain circuit therapeutics



Interventional



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}

Advanced training in interventional psychiatry

[Sina Nikayin](#) ✉ • [Joseph J. Taylor](#) ✉ • [Robert B. Ostroff](#) 👤 ✉

Published: December 15, 2021 • DOI: <https://doi.org/10.1016/j.jns.2021.120093> •  Check for updates

Clinical Commentary

The Electrochemical Brain: Lessons From *The Bell Jar* and Interventional Psychiatry

Joseph J. Taylor, Hedy Kober, and David A. Ross

Empirical Report | [Published: 20 February 2014](#)

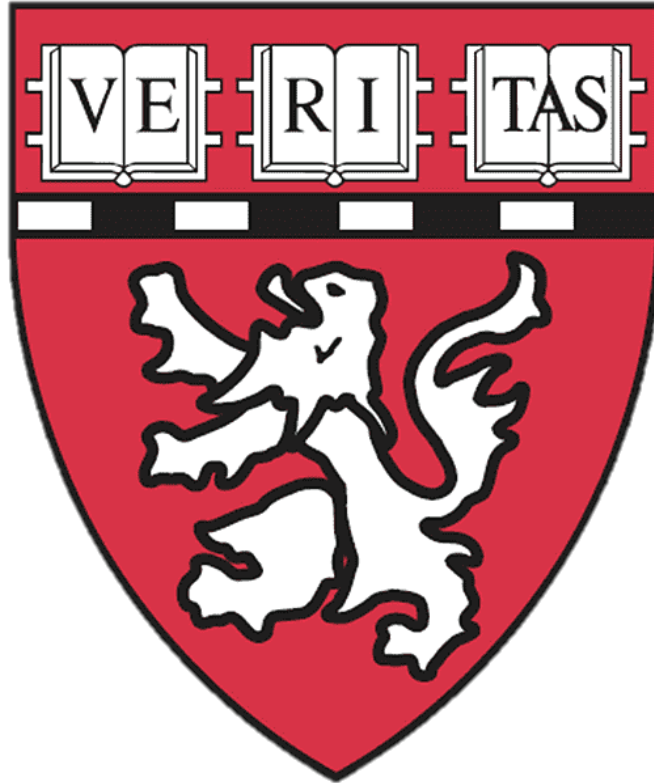
Interventional Psychiatry: How Should Psychiatric Educators Incorporate Neuromodulation into Training?

[Nolan R. Williams](#) ✉, [Joseph J. Taylor](#), [Jonathan M. Snipes](#), [E. Baron Short](#), [Edward M. Kantor](#) & [Mark S. George](#)

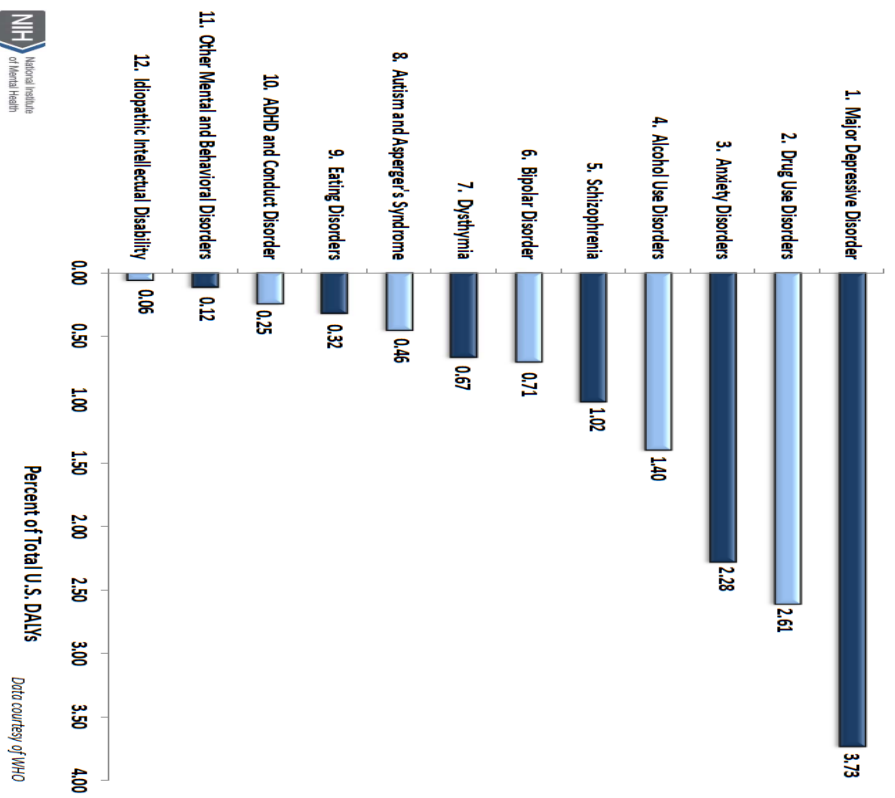
ARTICLE

An Interventional Psychiatry Track

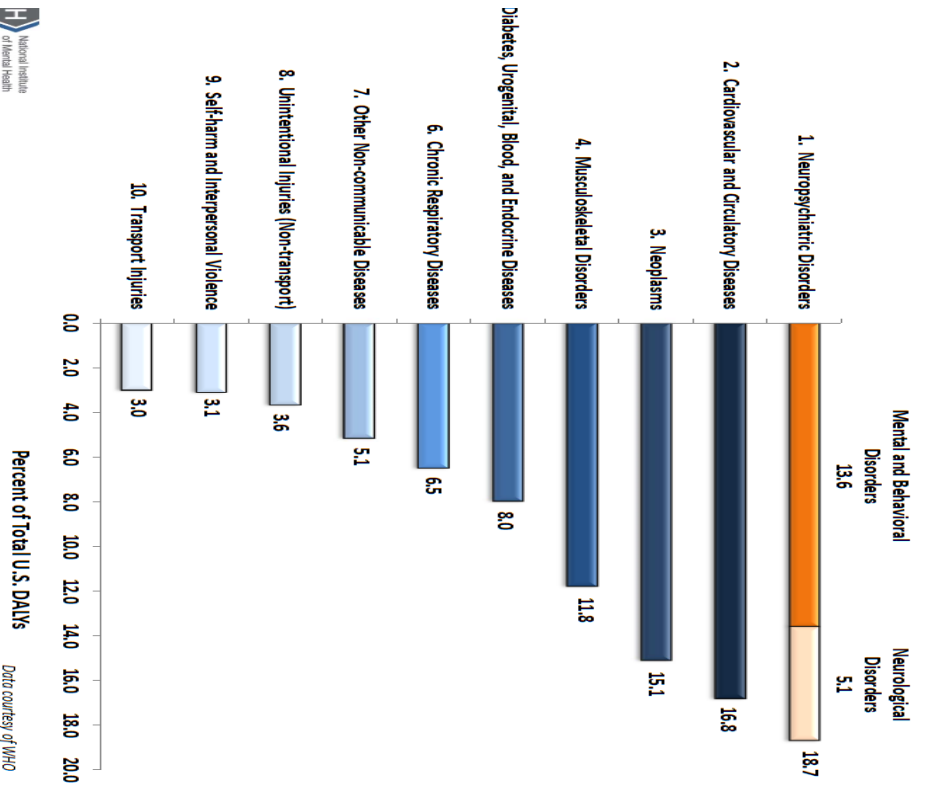
Joshua C. Brown, M.D., Ph.D.



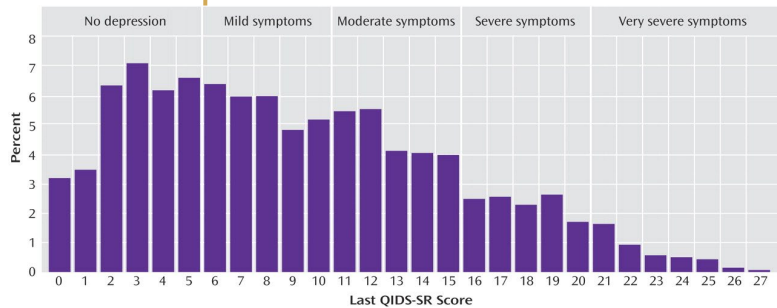
U.S. DALYs for Mental and Behavioral Disorders as a Percent of Total U.S. DALYs (2010)



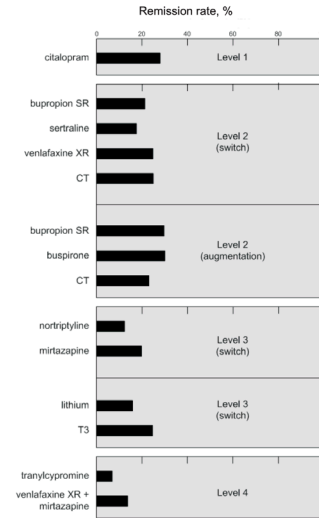
Top 10 Leading Disease/Disorder Categories Contributing to U.S. DALYs (2010)



2/3 still have symptoms after 3 months on an antidepressant

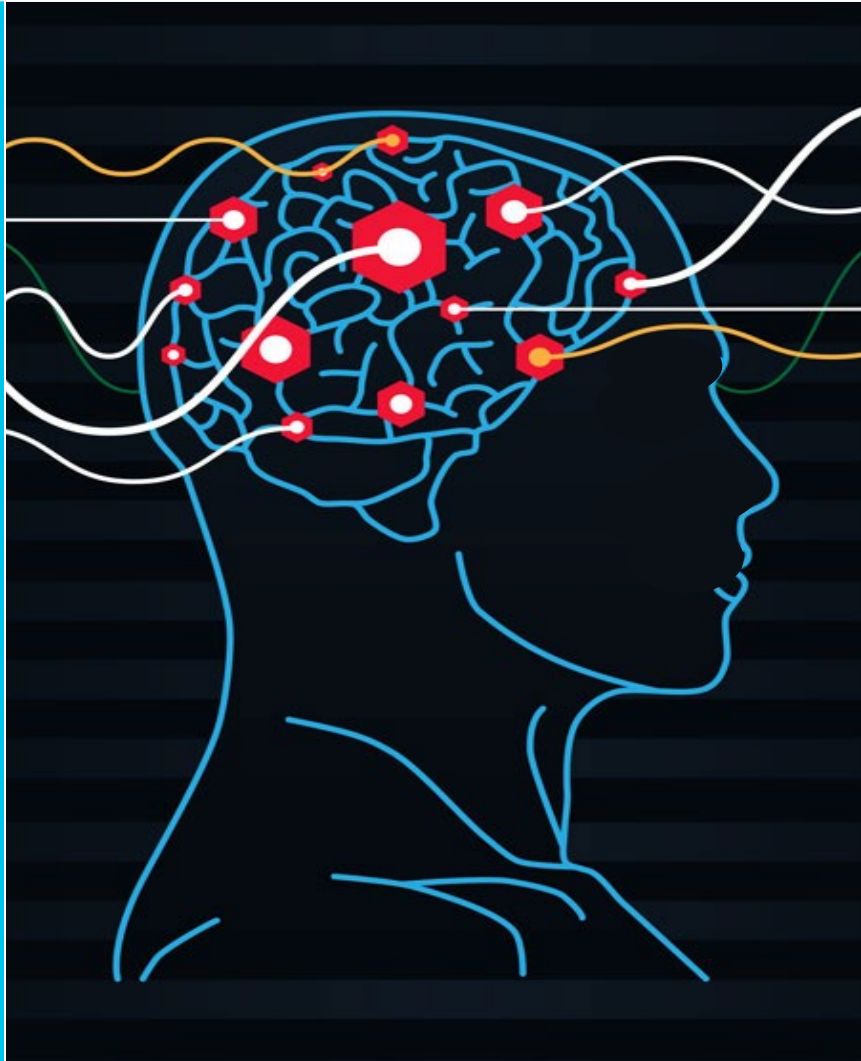


STAR*D Trial
N = 2806



Probability of getting well and staying well drops with each change or addition

Why Interventional Psychiatry?



Interventional Psychiatry



Towards accredited clinical training in brain stimulation: Proceedings from the Brain Stimulation Subspecialty Summits

Shan H. Siddiqi^{a b c d}  , Leo Chen^{e f}, Nicholas T. Trapp^{g h}, Noreen Bukhari-Parlakturk^{i j}, Joseph J. Taylor^{a b d}, Aaron D. Boes^{h k}, Joshua C. Brown^{c d l}, Tracy Barbour^{d m}, Joan A. Camprodon^{d m}, Michael D. Fox^{a b d n}, Brian H. Kopell^o, Carlene MacMillan^{p q r}, Alfonso Fasano^{s t u v}, Robert S. Fisher^w, Ziad Nahas^x, Gonzalo J. Revuelta^{y z}, Patricio Riva-Posse^{aa}, John D. Rolston^{a d bb}, Katherine Scangos^{cc dd}, Mouhsin M. Shafi^{d ee}... Nolan R. Williams^{hh}

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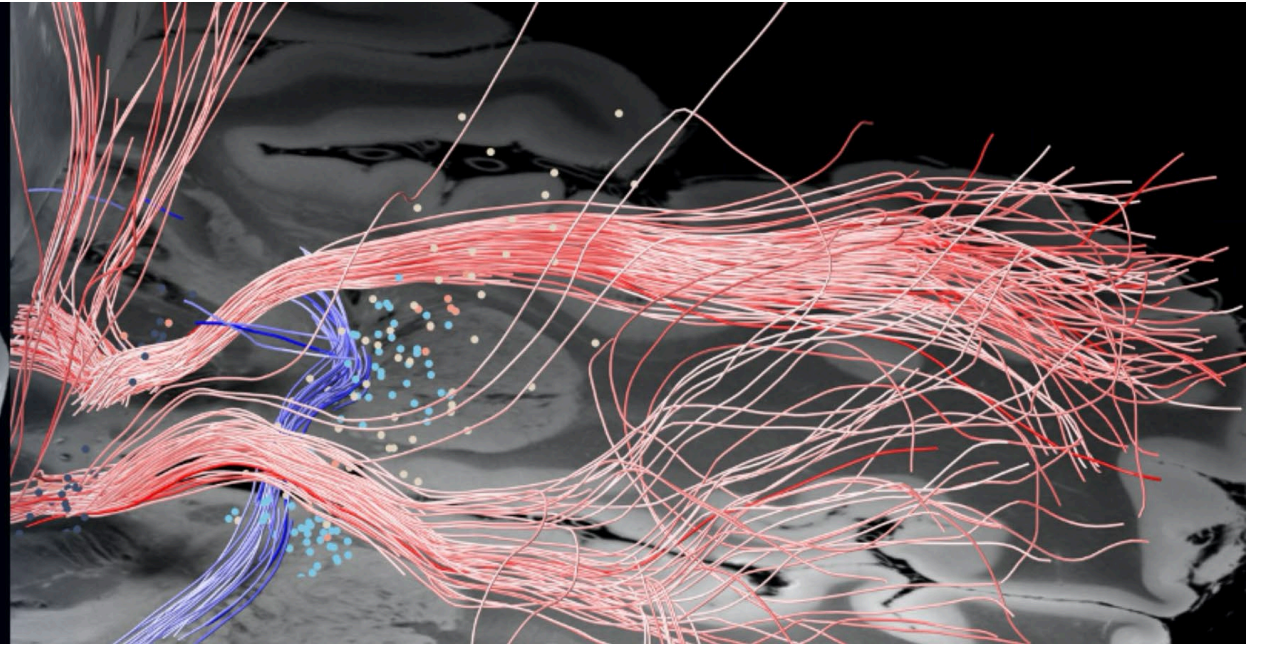
<https://doi.org/10.1016/j.brs.2025.02.012> 

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Center for Brain Circuit Therapeutics



REVIEW ARTICLE

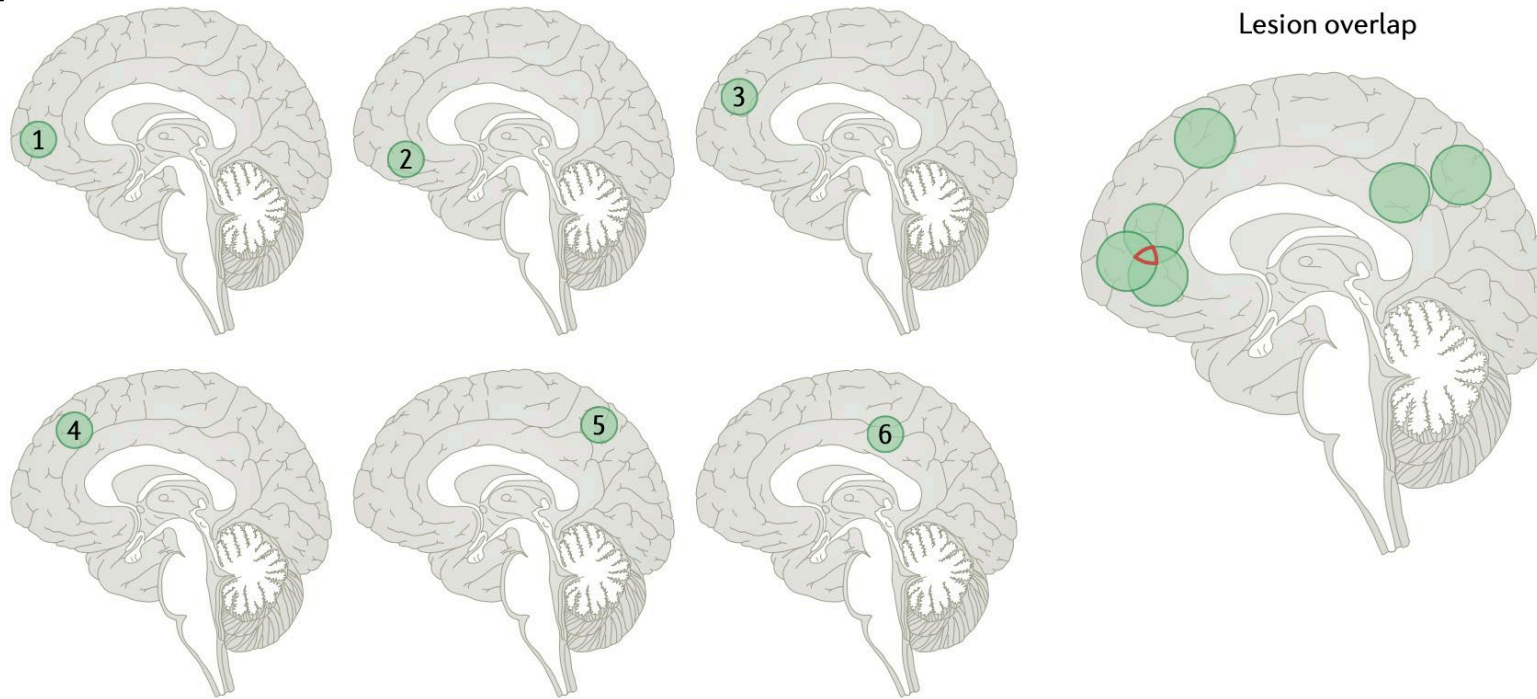
FRONTIERS IN MEDICINE

Mapping Symptoms to Brain Networks with the Human Connectome

Michael D. Fox, M.D., Ph.D.

THE STUDY OF FOCAL BRAIN LESIONS HAS TRADITIONALLY BEEN USED TO map neurologic symptoms to specific regions; however, many neurologic and psychiatric symptoms correspond more closely to networks of connected regions. A new resource termed the human connectome, derived from functional neuroimaging of thousands of healthy persons, provides a map of these brain connections. With the use of the connectome, lesions in different locations that cause the same symptom can be linked to common networks in ways not previously possible. This approach, termed lesion network mapping, is being applied to lesions associated with a variety of neuropsychiatric symptoms, including hallucinations, delusions, abnormal movements, pain, coma, and cognitive or social dysfunction (see the interactive graphic, available with the full text of this article at NEJM.org). Connectome localizations may expose new treatment targets for patients with complex neurologic and psychiatric symptoms. To appreciate this new approach to symptom localization, it is helpful to understand the evolution of classic lesion localization, functional imaging, the human brain connectome, and the analytic method of lesion network mapping.

a





Lesion network mapping for symptom localization: recent developments and future directions

Juho Joutsa^{a,b,*}, Daniel T. Corp^{c,d,*}, and Michael D. Fox^d

Purpose of review

Focal lesions causing specific neurological or psychiatric symptoms can occur in multiple different brain locations, complicating symptom localization. Here, we review lesion network mapping, a technique used to aid localization by mapping lesion-induced symptoms to brain circuits rather than individual brain regions. We highlight recent examples of how this technique is being used to investigate clinical entities and identify therapeutic targets.

Recent findings

To date, lesion network mapping has successfully been applied to more than 40 different symptoms or symptom complexes. In each case, lesion locations were combined with an atlas of human brain connections (the human connectome) to map heterogeneous lesion locations causing the same symptom to a common brain circuit. This approach has lent insight into symptoms that have been difficult to localize using other techniques, such as hallucinations, tics, blindsight, and pathological laughter and crying. Further, lesion network mapping has recently been applied to lesions that improve symptoms, such as tremor and addiction, which may translate into new therapeutic targets.

Summary

Lesion network mapping can be used to map lesion-induced symptoms to brain circuits rather than single brain regions. Recent findings have provided insight into long-standing clinical mysteries and identified testable treatment targets for circuit-based and symptom-based neuromodulation.

Keywords

connectivity, diaschisis, lesion, lesion network mapping, localization, network, neuroimaging, symptom

INTRODUCTION

Studying patients with focal brain lesions can provide unique insight into symptom localization as one can infer a causal link between the lesion location and the resulting symptoms [1]. As such, lesion-based studies have provided the foundation for symptom localization in neurology for more than a century. Lesion-based studies have advanced from individual cases to controlled data-driven whole brain analyses with sophisticated computational neuroimaging tools [2,3]. However, lesions causing similar symptoms often occur in heterogeneous brain locations with little overlap, leaving localization unclear [4,5]. One of the reasons for the lack of overlap is that lesions can also have a functional effect on remote but connected brain regions through disconnection or diaschisis, complicating efforts at lesion-based symptom localization [6,7]. Lesion network mapping (LNM) is one technique that has been introduced to help address this problem, with the goal of mapping brain lesions to brain circuits rather than individual brain regions [8]. The

underlying assumption is that symptoms map to a network with multiple foci in the brain and that a lesion anywhere in this network can result in emergence of the symptom. Since its introduction in 2015, LNM has grown in popularity (Fig. 1), and been utilized by a growing number of research groups. Previous reviews have focused on advances in lesion-mapping methods [9], mapping symptoms to brain circuits rather than individual regions [1],

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Correspondence to Dr Juho Joutsa, Turku Brain and Mind Center, Kinamyllyntkatu 10, Faculty of Medicine, Medisina A1, 20014 University of Turku, Turku, Finland. E-mail: jjout@utu.fi

*J.J. and D.T.C. contributed equally to the writing of this article.

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DOI:10.1097/WCO.00000000000001085

Table 1. Symptoms and functions localized by lesion network mapping to date

Motor and speech disorders		Nonmotor symptoms		Behavioral changes	
Akinetic mutism	Darby, 2018	Amnesia	Ferguson, 2019	Criminality	Darby, 2018
Alien limb	Darby, 2018	Anosognosia for hemiplegia	Klingbeil, 2020	Mind wandering	Philippi, 2021
Aphasia	Wawrzyniak, 2022	Autoscopic phenomena	Blondiaux, 2021	Pedophilia	Scarpazza, 2021
	Boes, 2015	Blindsight	Kletenik, 2022	Spirituality and religiosity	Ferguson, 2021
Central hypoventilation syndrome	Prabhakar, 2020	Bodily awareness disorders	Herbet, 2019		
Cervical dystonia	Corp, 2019	Bodily self-consciousness failure	Wawrzyniak, 2018		
Falling risk	Crockett, 2022	Cerebellar cognitive affective syndrome	Albazron, 2019		
Foreign accent syndrome	Higashiyama, 2021	Cognitive impairment	Reber, 2021		
Freezing of gait	Fasano, 2017		Crockett, 2021		
Infantile spasms	Cohen, 2021	Coma	Fischer, 2016		
Hemichorea	Laganiere, 2016	Decision-making impairment	Sutterer, 2016		
Holmes' tremor	Joutsa, 2019	Delusional misidentification	Darby, 2017	Improvement of symptoms	
Parkinsonism	Joutsa, 2018	Depression	Padmanabhan, 2019	Addiction remission	Joutsa, 2022
Poststroke motor outcomes	Lee, 2020	Epilepsy	Bdaiwi, 2021	Essential tremor improvement	Joutsa, 2018
Poststroke sensorimotor outcomes	Jimenez-Marin, 2021		Mansouri, 2020		
Step length asymmetry	Kyeong, 2021	Executive function impairment	Hwang, 2020		
Poststroke functional outcomes ^a	Bowren, 2022	Hallucinations	Boes, 2015		
	Cohen, 2021		Kim, 2021		
	Pini, 2021	Loss of consciousness	Snider, 2020		
	Salvalaggio, 2020	Mania	Cotovia, 2020		
Tics	Ganos, 2022		Lee, 2019		
		Pain	Boes, 2015		
			Elias, 2020		
		Pathological laughter and crying	Klingbeil, 2021		
		Prosopagnosia	Cohen, 2019		
		Spatial delusions	Alves, 2021		

Only first author and year of publication shown; full bibliographic references are located in Table S2, <http://links.lww.com/CONR/A66>.

^aStudies also assessed nonmotor outcomes.

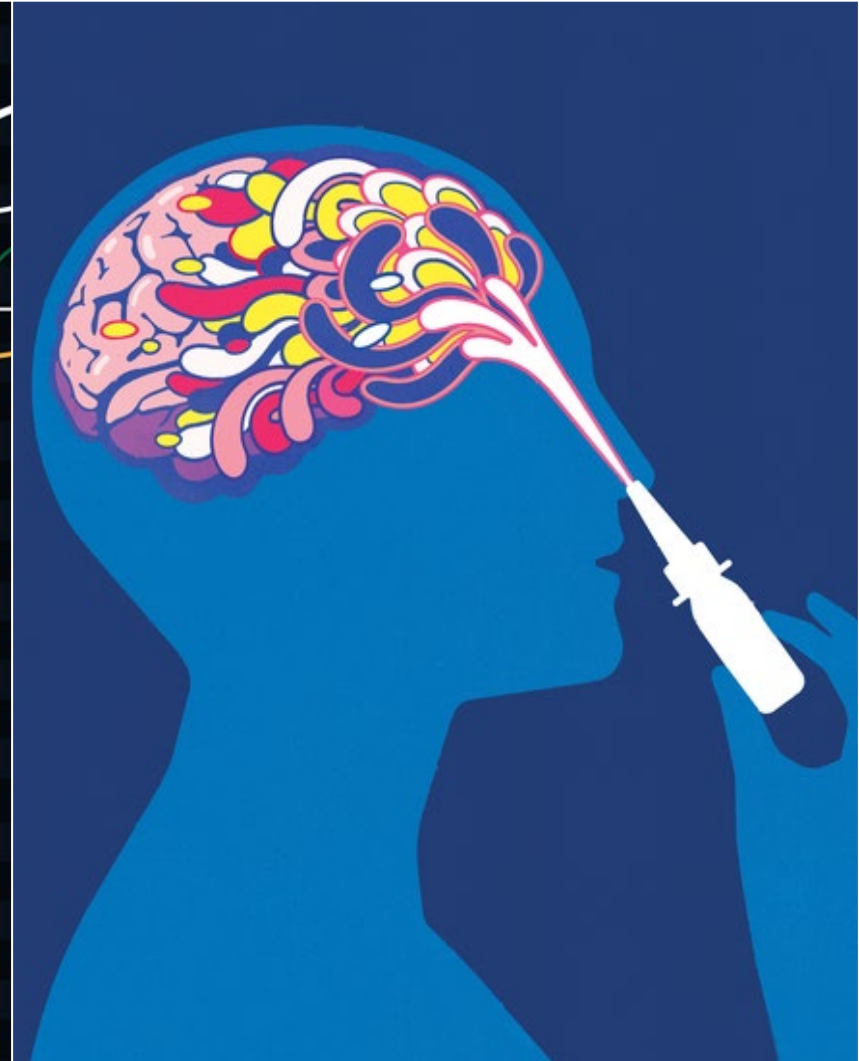
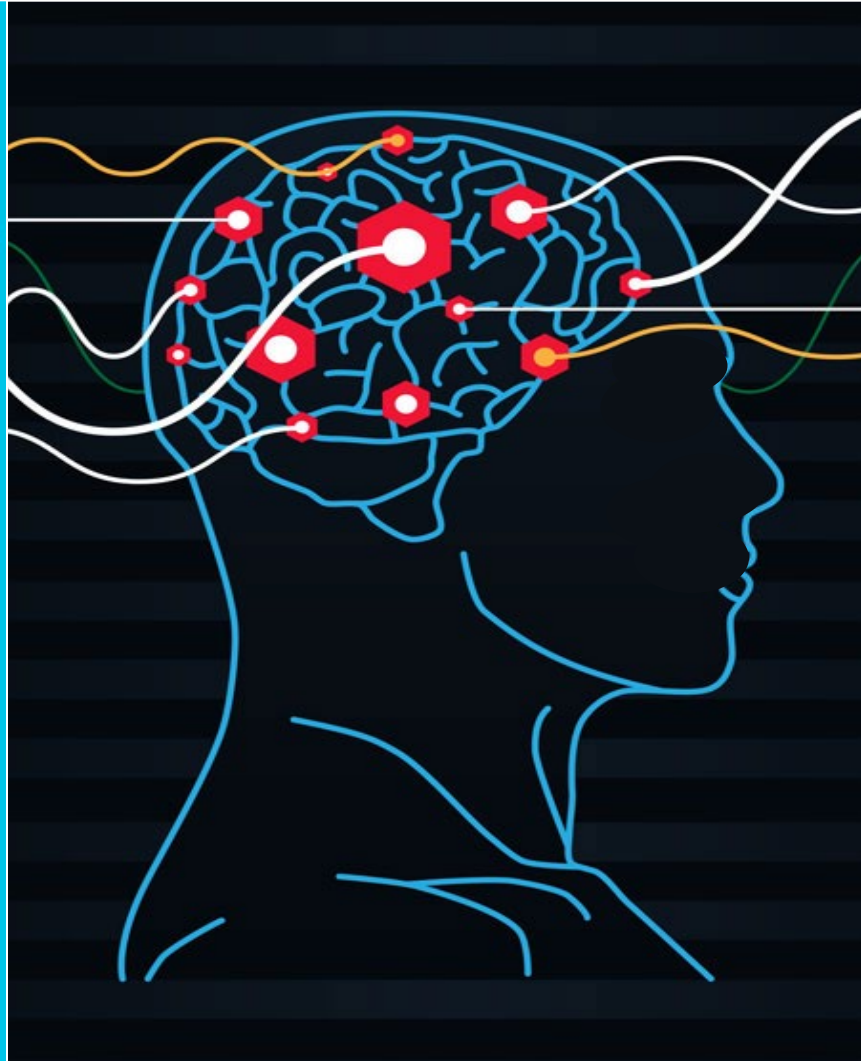
From circuit discovery to deployable treatment

Our platform identifies causal therapeutic brain circuits, localizes these circuits in individual patients, and translates them into deployable neuromodulation therapies

Disease- and device-agnostic

Therapies

ECT and TMS



ECT



“...because wherever I
sat — on the deck of a ship
or at a street café in Paris
or Bangkok — I would be
sitting under the same
glass bell jar, stewing in my
own sour air.”

A black and white portrait of Sylvia Plath, looking directly at the camera with a serious expression. Her hair is dark and shoulder-length. The background is slightly out of focus, showing what appears to be a bookshelf.

LETTERS TO THE EDITOR

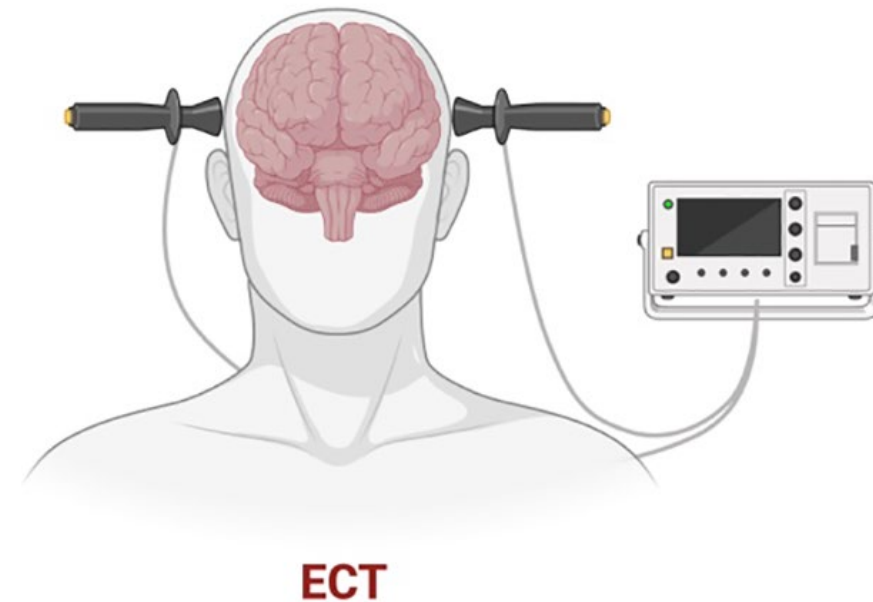
Sylvia Plath Recovered Completely by Electroconvulsive Therapy at the Age of 21 Years and Might Have Been Saved by Another Series 9 Years Later

Bergsholm, Per MD, PhD

[Author Information](#) ☑

ECT Basics

- Medically induced seizure under general anesthesia
- Among the oldest, most effective, and most stigmatized treatments in psychiatry
- Modify brain activity based on variables:
 - Where (electrode placement)
 - When (frequency of treatments)
 - How (protocol)
- **APA guidelines:** treatment-resistant depression, schizophrenia, schizoaffective disorders, catatonia



Modern ECT has changed more than its use has

Advances in efficacy, cognition, and relapse prevention have not translated into routine access

1.5%

**of general-hospital
inpatients with severe mood
disorders received ECT**

≈9 IN 10 U.S. hospitals did
not offer ECT

WHAT MODERN ECT CHANGED

~10 min

orientation recovery after ultra brief right-unilateral ECT

62%

remission in a large multisite study of geriatric depression

6.6% vs 12.3%

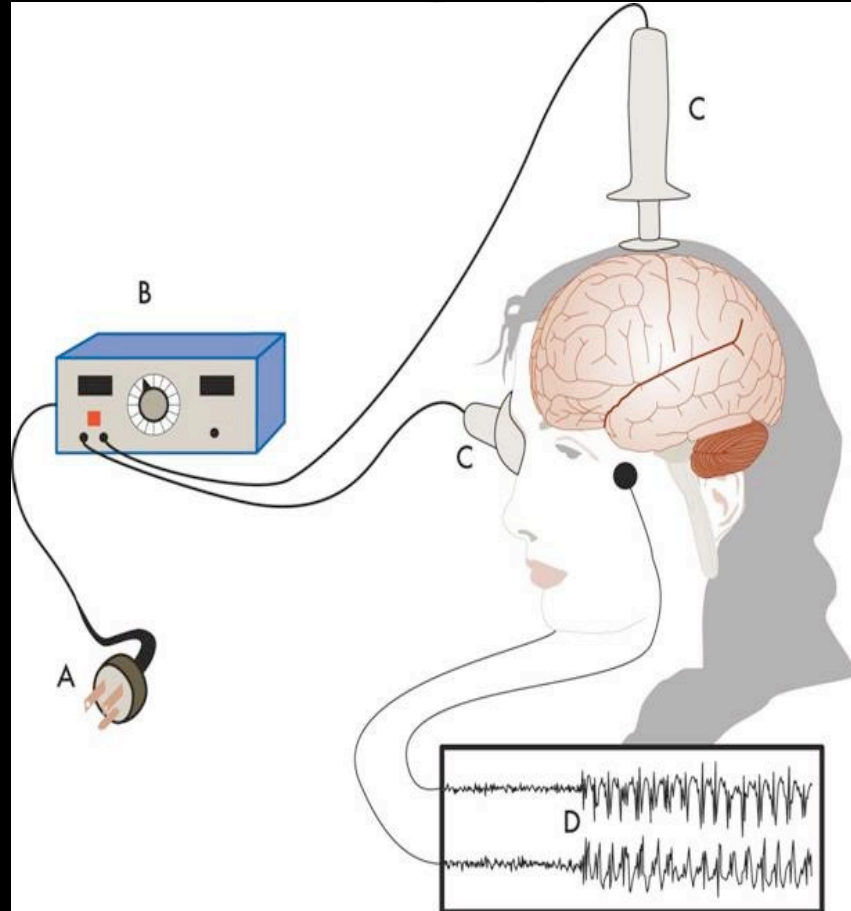
30-day readmission with vs without ECT

THE BOTTLENECK IS NOT THE EVIDENCE

Stigma, uneven availability, and economic/cultural/political forces continue to determine who receives a potentially life-altering treatment.

No Stigma

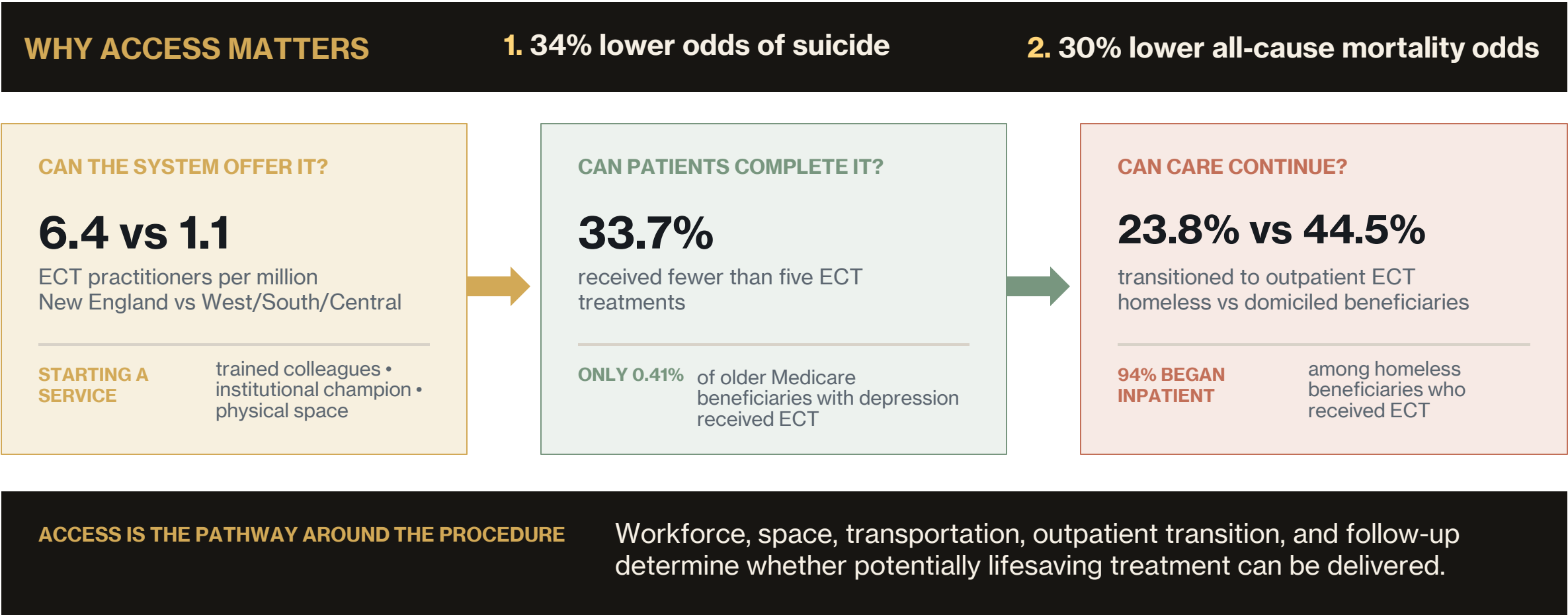
Stigma



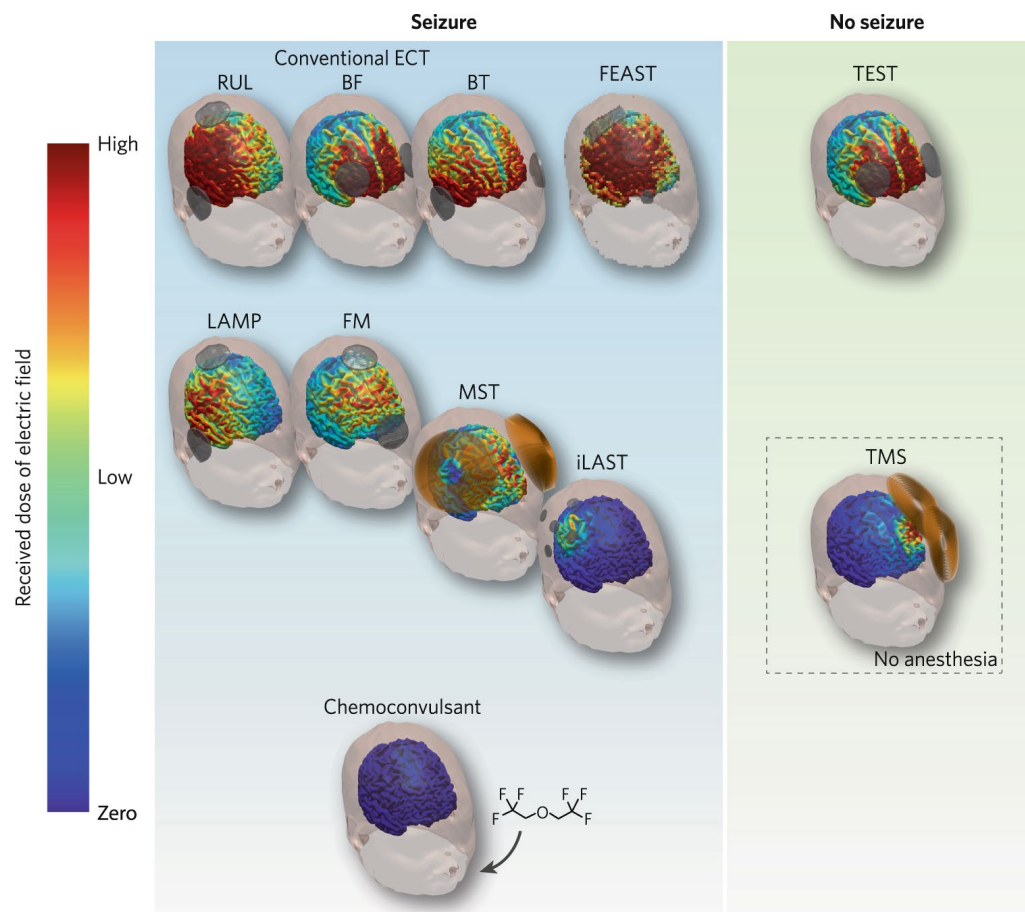
Stigma correlates with lead placement?

The stakes of ECT access extend beyond symptom relief

The treatment may reduce suicide and mortality, yet access can fail when a service is created, a course is delivered, or care moves outpatient.



Wilkinson et al., *Psych Serv.* 2021; Rhee et al., *J Clin Psych.* 2020;
Wilkinson et al., *Psych Q.* 2021; Odermatt et al., *Neurosci Appl.* 2025.



Confirmatory efficacy and safety trial of magnetic seizure therapy versus right unilateral ultra-brief electroconvulsive therapy in depression (CREST-MST): a randomised, double-blind, non-inferiority trial in Canada and the USA



Daniel M Blumberger, Shawn M McClintock, Kevin E Thorpe, Carol A Tamminga, Karen Foley, Mustafa M Husain, Tyler S Kaster, Yuliya Kryahnytska, Daphne Voineskos, Kala J Bailey, Joshua J Hubregsen, Cory R Weissman, Zafiris J Daskalakis

Summary

Background Magnetic seizure therapy (MST) is an innovative convulsive therapy that is clinically beneficial for patients with depression and has fewer cognitive adverse effects. This trial aimed to confirm the efficacy, tolerability, and cognitive safety of MST compared with right unilateral ultra-brief pulse-width (RUL-UB) electroconvulsive therapy (ECT).

Methods This multisite randomised, double-blind, parallel-group, non-inferiority trial was conducted at three academic centres across Canada and the USA. Participants aged 18 years and older with major depressive disorder (MDD) received treatment until they achieved remission, dropped out, or up to 21 total treatments. MST was delivered using a twin coil in a midline frontal position. Remission of depression on the Hamilton Rating Scale for Depression-24 item and worsening of autobiographical memory on the Autobiographical Memory Test (AMT) were the coprimary outcomes. The non-inferiority margin was 15% absolute difference in remission rates and AMT worsening was defined as 25% reduction, corresponding to one standard deviation reduction in performance. People with lived experience were not directly involved; the study was informed by indirect feedback from previous trials and clinical discussions with people with depression who declined ECT. The trial is registered with ClinicalTrials.gov, NCT03191058.

Findings Between June 26, 2018 and March 1, 2024, 292 participants were enrolled, of whom 239 were randomly assigned and three withdrew before treatment across study sites (RUL-UB ECT: mean age 45·5 years [SD 14·8, range 18–78], 80% White, 65 [55%] female, 54 [45%] male; MST: mean age 44·5 years [SD 13·8, range 18–75], 100 [85%] White, 70 [60%] female, 47 [40%] male). Enrolment concluded before reaching the intended sample size. The difference in remission rates was 5·3% in favour of RUL-UB ECT (27·8%) compared with MST (22·5%), establishing non-inferiority of MST (Z-test $p=0·048$ [95% CI –4·4 to 14·9]). More RUL-UB ECT participants had worsening autobiographical memory (17·3%) compared with MST participants (2·7%; $p=0·0003$). 12 participants in the RUL-UB ECT group and three participants in the MST group withdrew from treatment due to non-serious adverse events.

Interpretation MST showed non-inferior efficacy relative to RUL-UB ECT in achieving remission of depression, and a more favourable cognitive safety profile. Collectively, the overall risk–benefit profile of MST supports its consideration as a first-line convulsive therapy in MDD, particularly in those who refuse RUL-UB ECT.

Funding National Institutes of Mental Health.

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Introduction

A large proportion of individuals with major depressive disorder (MDD) experience treatment-resistant depression (TRD) and have little to no benefit from multiple medication trials.¹ Electroconvulsive therapy (ECT) is an effective treatment in patients with TRD,² yet only 1% accept treatment,^{3,4} due largely to negative perceptions and cognitive adverse effects⁵. In particular, ECT results in substantial post-ictal disorientation, and anterograde and retrograde amnesia.⁶ The extent of anterograde and retrograde amnesia remains

a considerable challenge for individuals and their families.⁷ Efforts to lessen the cognitive adverse effects of ECT while retaining its efficacy have led to treatment advancements such as right unilateral (RUL) and RUL ultra-brief pulse-width (RUL-UB) ECT.² RUL-UB ECT shows clinical efficacy in treating depression and fewer cognitive adverse effects, compared with both conventional bilateral forms of ECT⁸ and brief pulse RUL ECT.⁹ Nonetheless, the cognitive adverse effects associated with RUL and RUL-UB ECT continue to be a barrier to treatment acceptance.¹⁰

MST shifted the efficacy–cognition tradeoff?

Randomized, double-blind comparison with right-unilateral ultra brief ECT • 3 academic centers • 239 randomized participants

MST uses high-output magnetic stimulation to induce a therapeutic seizure with a more focal cortical electric field.

EFFICACY

Remission



5.3 percentage points favored ECT

Noninferiority met against a 15-point margin; 95% CI upper bound 14.9.

COGNITIVE SAFETY

Clinically meaningful worsening of autobiographical memory

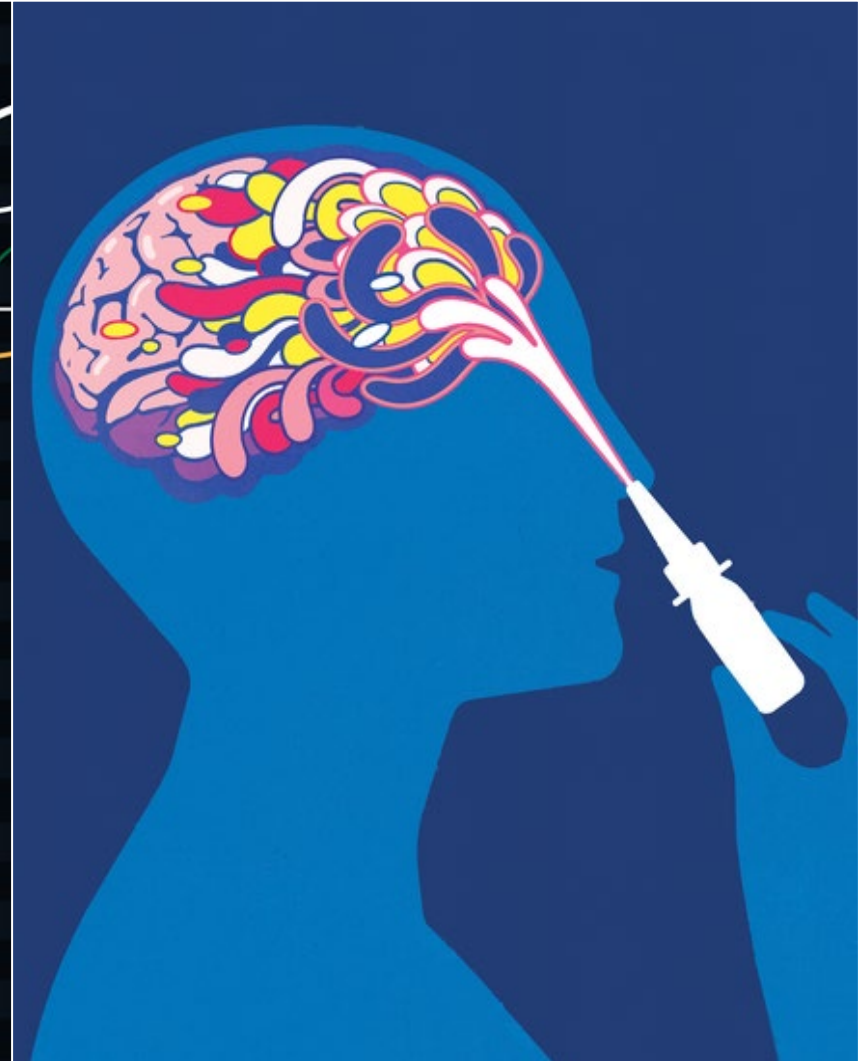
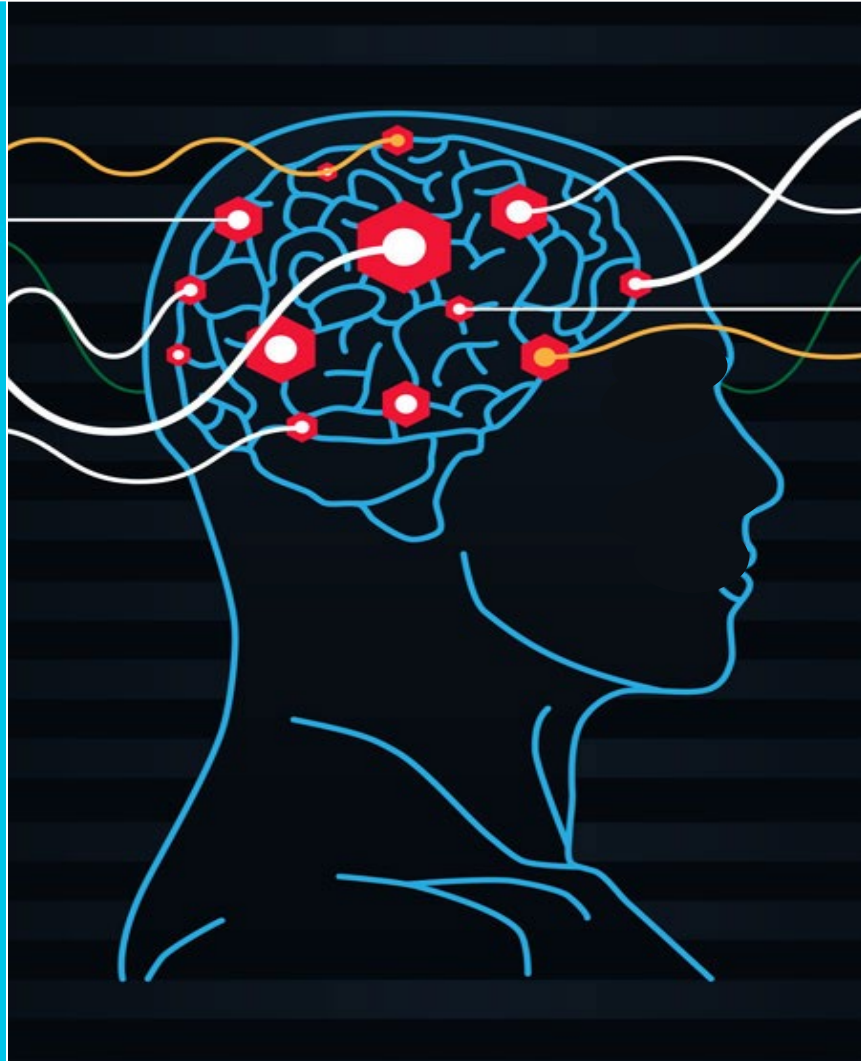


p = .0003

Withdrawals for non-serious adverse events

3 MST vs 12 ECT

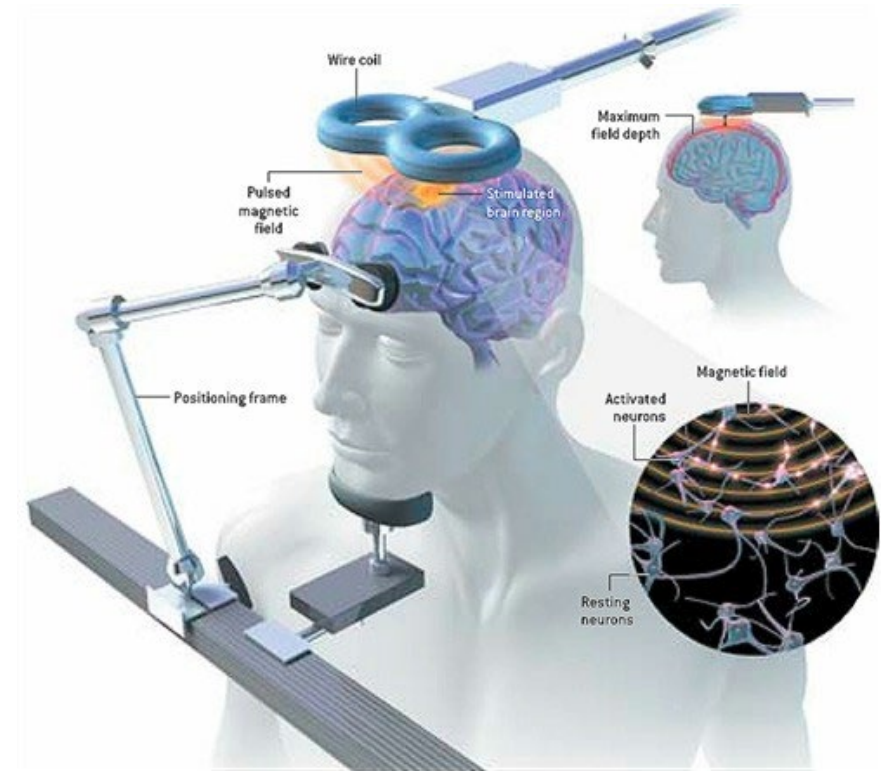
A DISTINCT RISK–BENEFIT PROFILE Especially relevant when cognitive concerns lead patients to decline ECT



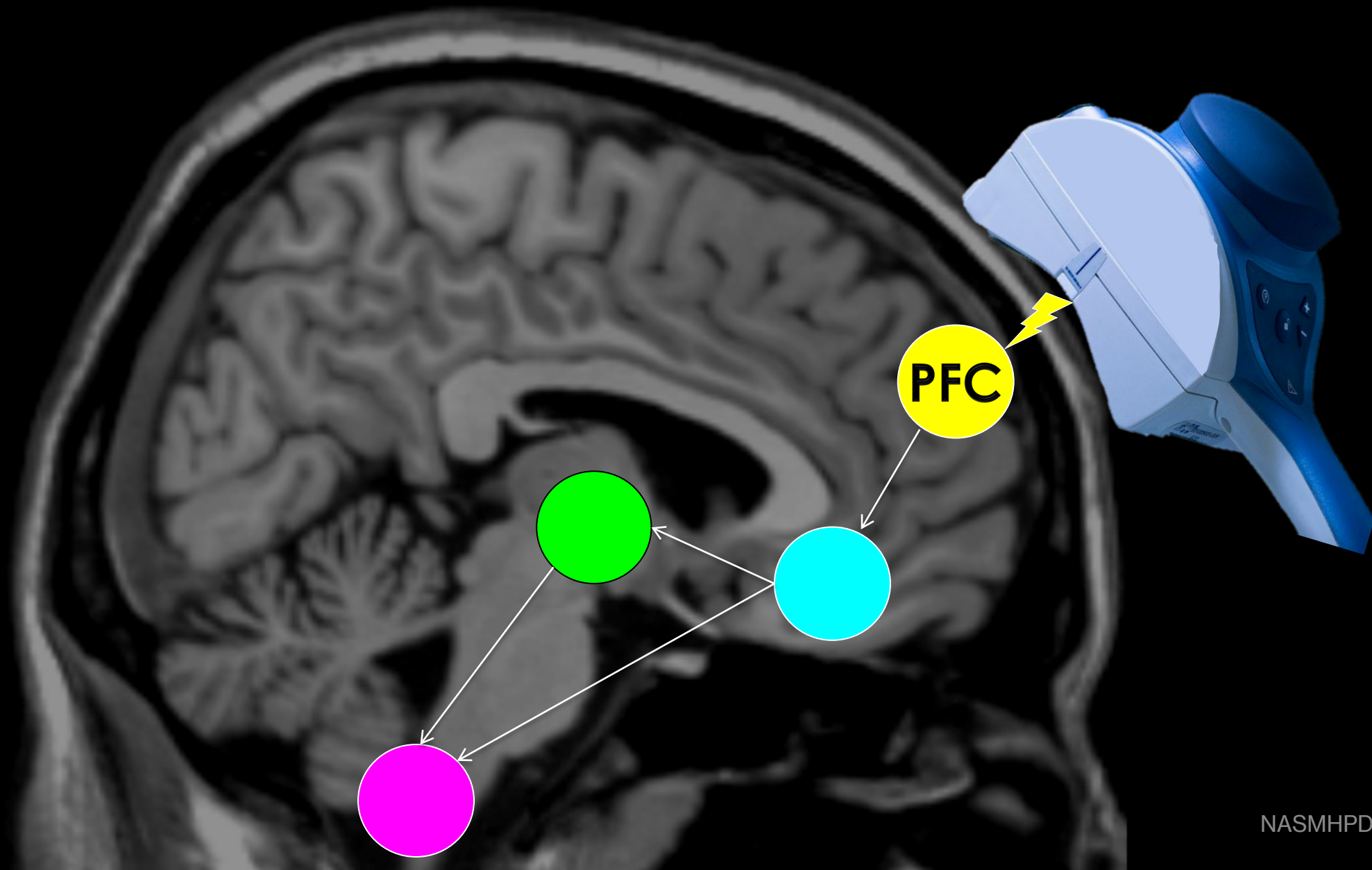
TMS

TMS Basics

- Focal, external stimulation via electromagnetic induction
- Modify brain activity based on variables:
 - Where (brain circuits)
 - When (state dependency)
 - How (protocol, coil shape)
- **FDA clearance:** treatment-resistant depression, “anxious depression,” migraine, OCD, smoking, PTSD
- **FDA Breakthrough Designation:** bipolar depression









E

Table 2

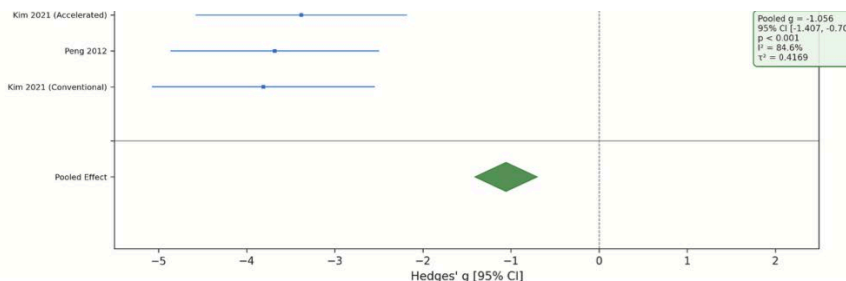
GRADE summary of findings.

Prefrontal rTMS versus sham stimulation for major depressive disorder. GRADE certainty ratings: HIGH (⊕⊕⊕⊕), MODERATE (⊕⊕⊕⊖), LOW (⊕⊕⊖⊖), VERY LOW (⊕⊖⊖⊖). RoB = risk of bias; OR = odds ratio; NNT = number needed to treat.

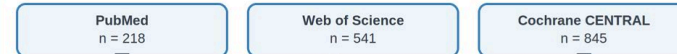
Outcome	k (N)	Effect [95% CI]	Clinical	I ²	RoB	GRADE factors	Certainty
Symptom severity (Hedges' g)	30 (1850)	g = -1.06 [-1.41, -0.70]	p < 0.001	84.6%	Serious (-1)	RoB (-1) Inconsistency (-1) Pub bias (-1)	VERY LOW ⊕⊖⊖⊖
Treatment response (OR)	20 (1221)	OR = 4.78 [3.08, 7.41]	NNT = 2.9	21.9%	Serious (-1)	RoB (-1) Large effect (+1)	HIGH ⊕⊕⊕⊕
Remission (OR)	11 (871)	OR = 3.55 [2.06, 6.13]	NNT = 4.4	34.5%	Serious (-1)	RoB (-1) Large effect (+1)	HIGH ⊕⊕⊕⊕
Dropout (OR)	16 (1350)	OR = 0.92 [0.63, 1.35]	p = 0.66	0.0%	Not serious	None	HIGH ⊕⊕⊕⊕

Note: The discrepancy between continuous (VERY LOW) and binary (HIGH) outcomes is driven by: (1) binary outcomes show much lower heterogeneity ($I^2 = 22\text{--}35\%$ vs 85%), (2) no significant publication bias for binary outcomes, and (3) large effect magnitude upgrade for binary outcomes ($OR > 2.5$). This pattern suggests that while the magnitude of symptom reduction is uncertain, the probability of achieving clinically meaningful response/remission is robustly established.

(Hedges' g = -1.056, 95% CI -1.4 to +0.31). Binary outcomes show 21.9%) and remission OR = 3.55. Meta-regression identified no significant difference between double-blind trials (C) and non-double-blind trials (C). **Conclusions:** Prefrontal rTMS robustly established for precision-oriented outcomes.



← Favors Active | Favors Sham →



Continuous outcome

k = 30 comparisons
N = 1,850
Hedges' g = -1.06

Binary outcomes

Response: k=20 (N=1,221)
Remission: k=11 (N=871)
OR = 4.78 / 3.55

rTMS as a Next Step in Antidepressant Nonresponders: A Randomized Comparison With Current Antidepressant Treatment Approaches

Iris Dalhuisen, Ph.D., Iris van Oostrom, Ph.D., Jan Spijker, M.D., Ph.D., Ben Wijnen, Ph.D., Eric van Exel, M.D., Ph.D., Hans van Mierlo, M.D., Ph.D., Dieuwertje de Waardt, M.D., Ph.D., Martijn Arns, Ph.D., Indira Tendolkar, M.D., Ph.D., Philip van Eijndhoven, M.D., Ph.D.

Objective: Although repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for depression, little is known about the comparative effectiveness of rTMS and other treatment options, such as antidepressants. In this multicenter randomized controlled trial, rTMS was compared with the next pharmacological treatment step in patients with treatment-resistant depression.

Methods: Patients with unipolar nonpsychotic depression (N=89) with an inadequate response to at least two treatment trials were randomized to treatment with rTMS or to a switch of antidepressants, both in combination with psychotherapy. Treatment duration was 8 weeks and consisted of either 25 high-frequency rTMS sessions to the left dorsolateral prefrontal cortex or a switch of antidepressant medication following the Dutch treatment algorithm. The primary outcome was change in depression severity based on the Hamilton Depression Rating Scale (HAM-D). Secondary outcomes were response and remission rates as well as change in symptom dimensions (anhedonia, anxiety, sleep, rumination,

and cognitive reactivity). Finally, expectations regarding treatment were assessed.

Results: rTMS resulted in a significantly larger reduction in depressive symptoms than medication, which was also reflected in higher response (37.5% vs. 14.6%) and remission (27.1% vs. 4.9%) rates. A larger decrease in symptoms of anxiety and anhedonia was observed after rTMS compared with a switch in antidepressants, and no difference from the medication group was seen for symptom reductions in rumination, cognitive reactivity, and sleep disorders. Expectations regarding treatment correlated with changes in HAM-D scores.

Conclusions: In a sample of patients with moderately treatment-resistant depression, rTMS was more effective in reducing depressive symptoms than a switch of antidepressant medication. In addition, the findings suggest that the choice of treatment may be guided by specific symptom dimensions.

Am J Psychiatry 2024; 181:806–814; doi: 10.1176/appi.ajp.20230556

Comparative effectiveness research trial for antidepressant incomplete and non-responders with treatment resistant depression (ASCERTAIN-TRD) a randomized clinical trial

George I. Papakostas¹, Madhukar H. Trivedi², Richard C. Shelton³, Dan V. Iosifescu⁴, Michael E. Thase⁵, Manish K. Jha⁶, Sanjay J. Mathew⁶, Charles DeBattista⁷, Mehmet E. Dokucu⁸, Olga Brawman-Mintzer⁹, Glenn W. Currier¹⁰, William Vaughn McCall¹¹, Mandana Modirrousta¹², Matthew Macaluso^{3,13}, Alexander Bystritsky¹⁴, Fidel Vila Rodriguez¹⁵, Erik B. Nelson¹⁶, Albert S. Yeung¹, Anna Feeney¹, Leslie C. MacGregor¹, Thomas Carmody² and Maurizio Fava¹

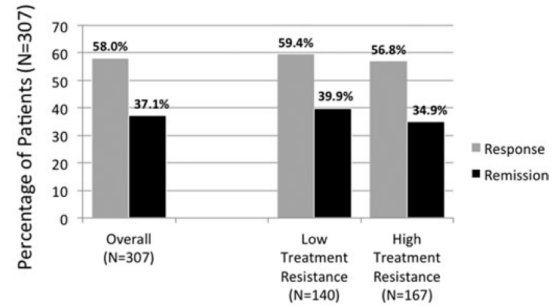
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Further research is needed to help improve both the standard of care and the outcome for patients with treatment-resistant depression. A particularly critical evidence gap exists with respect to whether pharmacological or non-pharmacological augmentation is superior to antidepressant switch, or vice-versa. The objective of this study was to compare the effectiveness of augmentation with aripiprazole or repetitive transcranial magnetic stimulation versus switching to the antidepressant venlafaxine XR (or duloxetine for those not eligible to receive venlafaxine) for treatment-resistant depression. In this multi-site, 8-week, randomized, open-label study, 278 subjects (196 females and 82 males, mean age 45.6 years (SD 15.3)) with treatment-resistant depression were assigned in a 1:1:1 fashion to treatment with either of these three interventions; 235 subjects completed the study. 260 randomized subjects with at least one post-baseline Montgomery-Asberg Depression Rating (MADRS) assessment were included in the analysis. Repetitive transcranial magnetic stimulation (score change (standard error (se)) = -17.39 (1.3) ($p = 0.015$) but not aripiprazole augmentation (score change (se) = -14.9 (1.1) ($p = 0.069$) was superior to switch (score change (se) = -13.22 (1.1)) on the MADRS. Aripiprazole (mean change (se) = -37.79 (2.9) ($p = 0.003$) but not repetitive transcranial magnetic stimulation augmentation (mean change (se) = -42.96 (3.6) ($p = 0.031$) was superior to switch (mean change (se) = -34.45 (3.0)) on the symptoms of depression questionnaire. Repetitive transcranial magnetic stimulation augmentation was shown to be more effective than switching antidepressants in treatment-resistant depression on the study primary measure. In light of these findings, clinicians should consider repetitive transcranial magnetic stimulation augmentation early-on for treatment-resistant depression.

Trial registration: ClinicalTrials.gov, NCT02977299

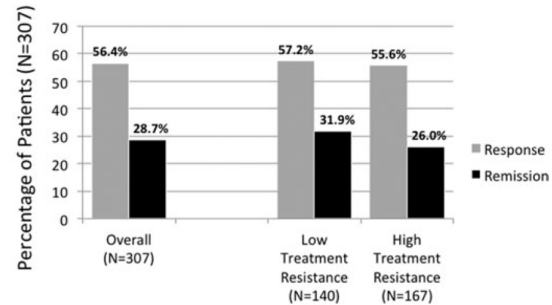
Molecular Psychiatry; <https://doi.org/10.1038/s41380-024-02468-x>

CGI-S Outcomes



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

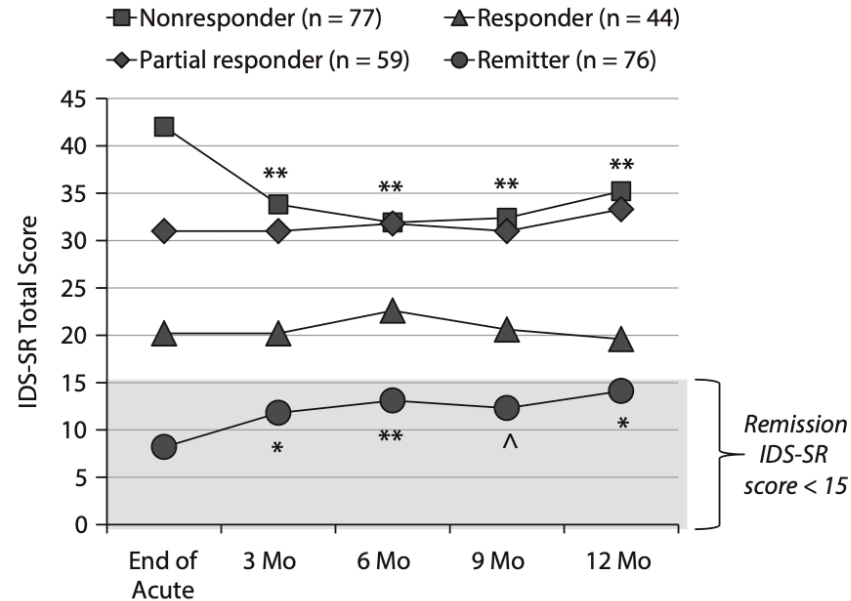
PHQ-9 Outcomes



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

Dunner et al

Figure 2. Summary of IDS-SR Total Score Outcomes During Long-Term Follow-Up: Stratification by End of Acute Treatment Clinical Outcome (N = 257)^a



TMS Effectiveness and Durability

Research Article

For reprint orders, please contact: info@becaris.com

Resource utilization and economic outcomes following repetitive magnetic stimulation for treatment-resistant depression: a retrospective observational analysis

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Aim: We investigated the impact of repetitive transcranial magnetic stimulation (rTMS) on healthcare resource utilization as well as payer costs. **Materials & methods:** We conducted a retrospective Medicare Fee-for-Service datasets and commercial (Medicare) from 1 January 2021 to 30 September 2023. We identified a cohort not treated with rTMS over an 18-month period. We compared the baseline characteristics of the cohorts, and we calculated amounts from Merative MarketScan Research Databases to the non-TMS cohort, the rTMS cohort incurred 37% (p < 0.0001) with 7% higher outpatient cost (\$8946 vs \$8300), incurred 24% fewer inpatient admissions (0.25 vs 0.33; p = 0.0392), 48% fewer emergency room costs (\$5666 vs \$6978; p = 0.0392), 48% fewer emergency room costs (\$322 vs \$487; p < 0.0001), and 18% fewer high acuity hospital visits. This study suggests that patients who receive rTMS for treatment-resistant depression (TRD) receive rTMS. From this perspective, rTMS is an investment through fewer high acuity hospital visits.

Plain language summary

What was the aim of this research? To assess whether repetitive transcranial magnetic stimulation (rTMS) reduces healthcare costs for treatment-resistant depression (TRD) over an 18-month timeframe. We tracked inpatient admissions, emergency room visits, and high acuity hospital visits.

What methodology is used in this study? We identified a cohort of patients who received rTMS for TRD and compared their healthcare costs to a non-TMS cohort who were comparable.

What were the results? Patients treated with rTMS cost 37% less than those treated with TMS.

What do the results tell us about rTMS for TRD?

Prices for new US drugs doubled in 4 years as focus on rare disease grows

By Deena Beasley

May 22, 2025 8:58 AM EDT · Updated May 22, 2025



U.S. dollar banknote and medicines are seen in this illustration taken, June 27, 2024. REUTERS/Dado Ruvic/Illustration/File Photo [Purchase Licensing Rights](#)

Summary Companies

- Median annual list price for new drugs over \$370,000 in 2024
- 72% of new drugs in 2024 for orphan diseases
- Drugmakers emphasize value, offer savings programs amid rising list prices

system utilization and

observational analysis of
icare Fee-for-Service
(3)

es:

ers less money

patients received TMS

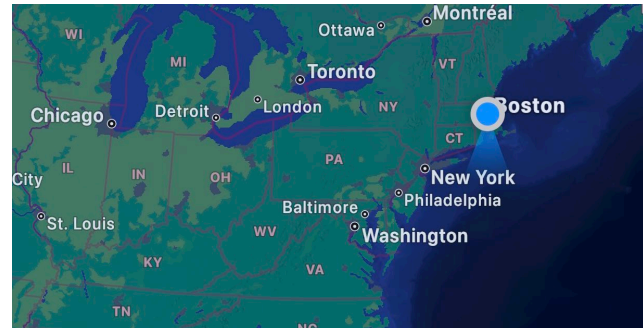
Conventional TMS Limitations

Time burden



6-8 Weeks

Target uncertainty



Scalp-based targeting

Response Limits



~50% are $\geq 50\%$ better



SAINT: Hope for new treatment of depression



NOVEMBER 7, 2021 / 9:17 AM / CBS NEWS

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

Eleanor J. Cole, Ph.D., Angela L. Phillips, Ph.D., Brandon S. Bentzley, M.D., Ph.D., Katy H. Stimpson, B.S., Romina Nejad, M.S., Fahim Barnak, M.D., Clive Veerapal, B.S., Naushaba Khan, B.S., Kirsten Cherian, Ph.D., Emily Felber, M.S., Randi Brown, M.S., Elizabeth Choi, M.S., Sinead King, Ph.D., Heather Pankow, B.S., James H. Bishop, Ph.D., Azeezat Azeez, Ph.D., John Coetzee, Ph.D., Rachel Rapier, B.S., Nicole Odenwald, M.A., David Carreon, M.D., Jessica Hawkins, B.A., Maureen Chang, B.S., Jennifer Keller, Ph.D., Kristin Raj, M.D., Charles DeBattista, M.D., Boool Jo, Ph.D., Flint M. Espil, Ph.D., Alan F. Schatzberg, M.D., Keith D. Sudheimer, Ph.D., Nolan R. Williams, M.D.

Objective: Depression is the leading cause of disability worldwide, and half of patients with depression have treatment-resistant depression. Intermittent theta-burst stimulation (iTBS) is approved by the U.S. Food and Drug Administration for the treatment of treatment-resistant depression but is limited by suboptimal efficacy and a 6-week duration. The authors addressed these limitations by developing a neuroscience-informed accelerated iTBS protocol, Stanford neuromodulation therapy (SNT; previously referred to as Stanford accelerated intelligent neuromodulation therapy, or SAINT). This protocol was associated with a remission rate of ~90% after 5 days of open-label treatment. Here, the authors report the results of a sham-controlled double-blind trial of SNT for treatment-resistant depression.

Methods: Participants with treatment-resistant depression currently experiencing moderate to severe depressive episodes were randomly assigned to receive active or sham SNT. Resting-state functional MRI was used to individually target the region of the left dorsolateral prefrontal cortex

most functionally anticorrelated with the subgenual anterior cingulate cortex. The primary outcome was score on the Montgomery-Åsberg Depression Rating Scale (MADRS) 4 weeks after treatment.

Results: At the planned interim analysis, 32 participants with treatment-resistant depression had been enrolled, and 29 participants who continued to meet inclusion criteria received either active (N=14) or sham (N=15) SNT. The mean percent reduction from baseline in MADRS score 4 weeks after treatment was 52.5% in the active treatment group and 11.1% in the sham treatment group.

Conclusions: SNT, a high-dose iTBS protocol with functional-connectivity-guided targeting, was more effective than sham stimulation for treatment-resistant depression. Further trials are needed to determine SNT's durability and to compare it with other treatments.

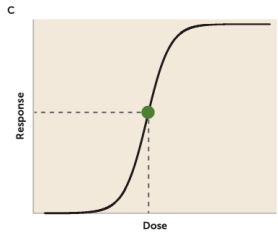
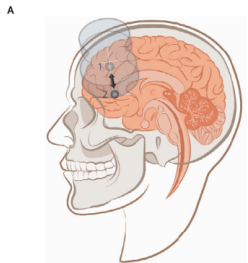
Am J Psychiatry 2022; 179:132–141; doi: 10.1176/appi.ajp.2021.20101429

Major depressive disorder is the leading cause of disability worldwide (1, 2), and approximately 50% of patients meet criteria for treatment-resistant depression (3). Repetitive transcranial magnetic stimulation (rTMS), a brain stimulation treatment approved by the U.S. Food and Drug Administration (FDA) for treatment-resistant depression (4–6), targets the left dorsolateral prefrontal cortex (DLPFC), a key area in neural circuitry underlying depressive symptoms that has been shown to be hypoactive in major depressive disorder (7–9). Contemporary FDA-approved protocols for stimulation of the left DLPFC are limited by the long duration of treatment course (6 weeks) (10) and have been only

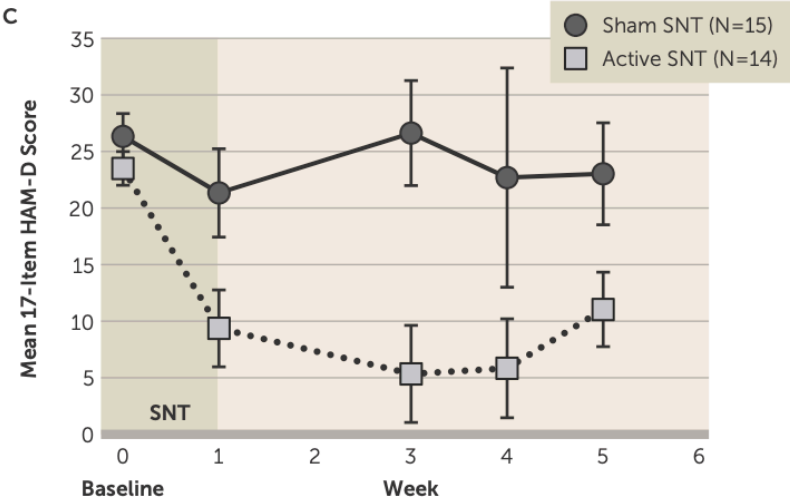
modestly effective, inducing remission after 4–6 weeks of treatment in ~17% of patients who have not shown response to three prior antidepressant treatments (11).

We developed an accelerated, high-dose, patterned, functional connectivity MRI (fcMRI)-guided rTMS protocol aimed at optimizing the treatment of treatment-resistant depression using neuroscience-informed stimulation parameters (12, 13). Our protocol, previously referred to as Stanford accelerated intelligent neuromodulation therapy (SAINT) and now entitled Stanford neuromodulation therapy (SNT), includes 1) an efficient form of rTMS, termed intermittent theta-burst stimulation (iTBS) (14); 2) treatment

See related features: **Editorials** by Dr. Nemeroff (p. 83) and by Drs. Weissman and Daskalakis (p. 85) and **CME course** (online and p. 141)

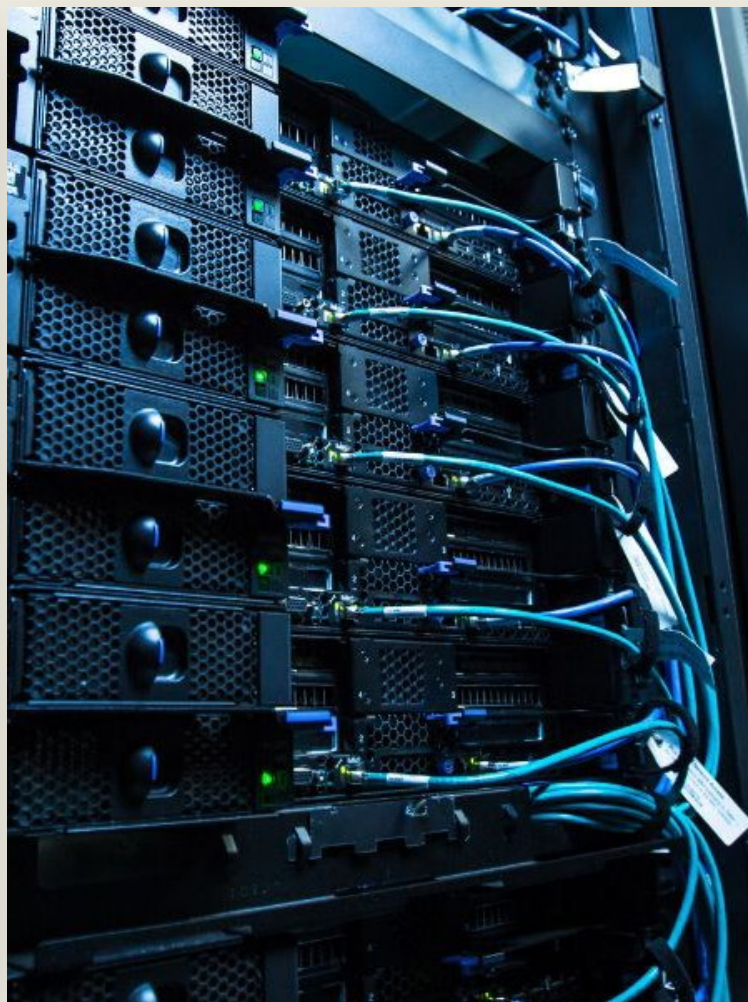


Day 1	Day 2	Day 3	Day 4	Day 5
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
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50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
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0889T	Personalized target development for accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation derived from a structural and resting-state functional MRI, including data preparation and transmission, generation of the target, motor threshold-starting location, neuronavigation files and target report, review and interpretation	S	1511
0890T	Accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation, including target assessment, initial motor threshold determination, neuronavigation, delivery and management, initial treatment day	S	1522
0891T	Accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation, including neuronavigation, delivery and management, subsequent treatment day	S	1522
0892T	Accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation, including neuronavigation, delivery and management, subsequent motor threshold redetermination with delivery and management, per treatment day	S	1522

Scalability and Non-Specific Effects



EDITORIAL

A New Era of Precision Neuromodulation in Psychiatry

Burak Uzay, MD, PhD; Helen S. Mayberg, MD; Martijn Figee, MD, PhD

ARTICLE

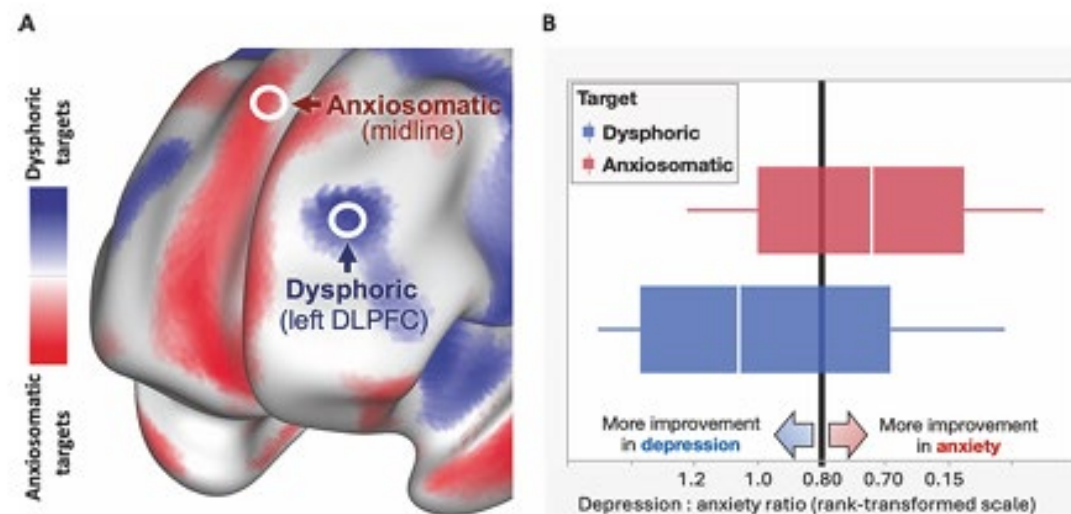
Circuit-targeted modulation of anxiety symptoms in individuals with major depression: A randomized head-to-head TMS trial

Joseph J. Taylor^{1,2,3}, Jing Li^{2,4}, Christopher Lin^{2,4}, Emma Jones^{2,3}, Summer Frandsen^{1,2,4}, Claudia R. Becker⁵, William Drew^{2,4}, Dania Haj-Darwish^{2,4}, Sandrine Jabbour^{2,4}, Jessica Leach^{2,4}, Stephan Palm^{1,2,4}, Lauren Sanderson^{2,4}, Emanuella Santos^{2,4}, Lera Sterina^{2,3}, Nicole Chiulli^{2,3}, John Miller^{1,4}, Sheena Barantono^{1,2,4}, Irene Gonsalvez^{1,2,3}, Stanley Lyndon^{1,2,3}, Samuel B. Snider^{1,2,4}, Michael D. Fox^{1,2,3,4,6} and Shan H. Siddiqi^{1,2,3,6}

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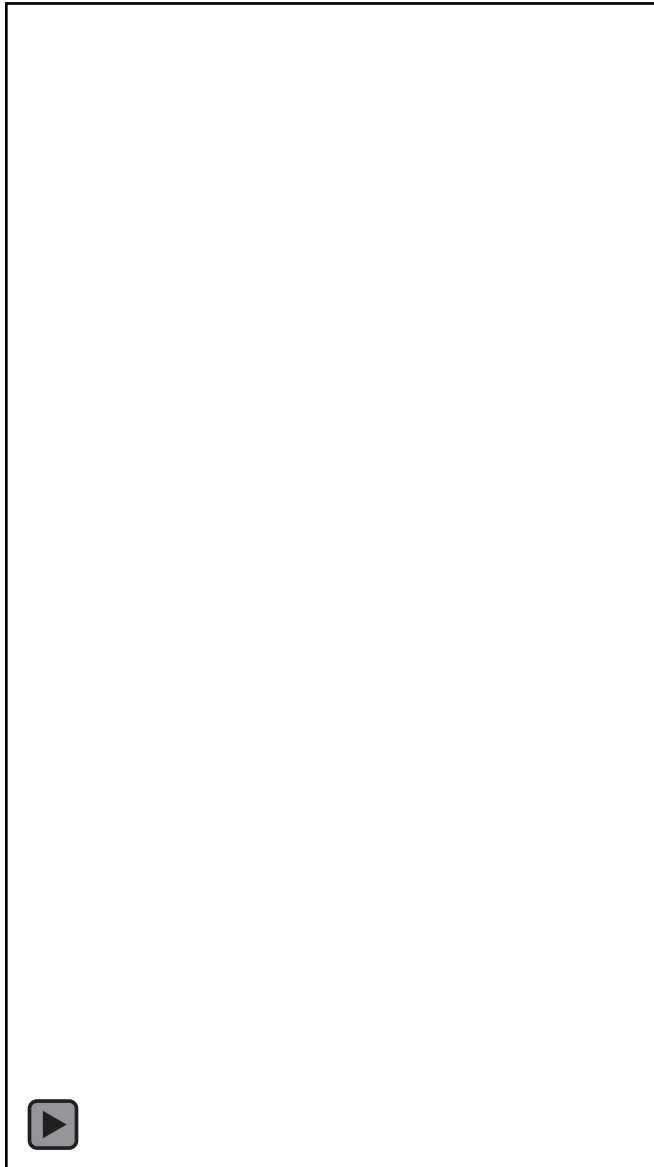
Transcranial magnetic stimulation (TMS) is effective for major depressive disorder (MDD) and anxious depression despite imprecise scalp-based targeting. Retrospective connectomics analyses suggest that targeting one brain circuit preferentially improves “dysphoric” symptoms, while targeting a different brain circuit preferentially improves “anxiosomatic” symptoms. Here, we tested this hypothesis prospectively by randomizing adults with MDD ($n = 40$, age 18–65) who had moderate-to-severe symptoms of depression (Beck Depression Inventory (BDI) ≥ 20) and anxiety (Beck Anxiety Inventory (BAI) ≥ 16) to a 30-treatment TMS course at the dysphoric circuit target (MNI coordinates $[-32, 44, 34]$, close to the conventional left dorsolateral prefrontal cortex target for MDD), or at the anxiosomatic circuit target (MNI coordinates $[0, 48, 46]$, a dorsomedial target not routinely used). As hypothesized, dysphoric circuit targeting ($n = 16$) improved BDI more than BAI (ratio 1.08, IQR 0.69–2.02), while anxiosomatic circuit targeting ($n = 20$) improved BAI more than BDI (ratio 0.70, IQR 0.01–1.01) (Wilcoxon rank-sum test $p = 0.0195$). Both targets improved BDI (55 vs 54%), but BAI improved significantly more with anxiosomatic circuit targeting (58 vs 36%, $p = 0.0301$), even when controlling for BDI ($p < 0.001$). Thus, TMS targeting different connectome-derived brain circuits differentially modulates anxiety that is comorbid with major depressive disorder. Future studies could target according to baseline symptom profile, a step toward precision psychiatry. **Trial Registration Number** NCT04604210.

Molecular Psychiatry; <https://doi.org/10.1038/s41380-026-03535-1>



Bringing Human Brain Connectomics to Clinical Practice in Psychiatry

Shan H. Siddiqi, Joseph J. Taylor, Andreas Horn, and Michael D. Fox



Efficacy of Adjunctive D-Cycloserine to Intermittent Theta-Burst Stimulation for Major Depressive Disorder

A Randomized Clinical Trial

Jaeden Cole, BSc^{1,2,3}; Maya N. Sohn, BSc^{1,2,3}; Ashley D. Harris, PhD^{2,3,4,5};
Signe L. Bray, PhD^{2,3,4}; Scott B. Patten, MD, PhD^{1,2,3,6}; Alexander McGirr, MD, PhD^{1,2,3}

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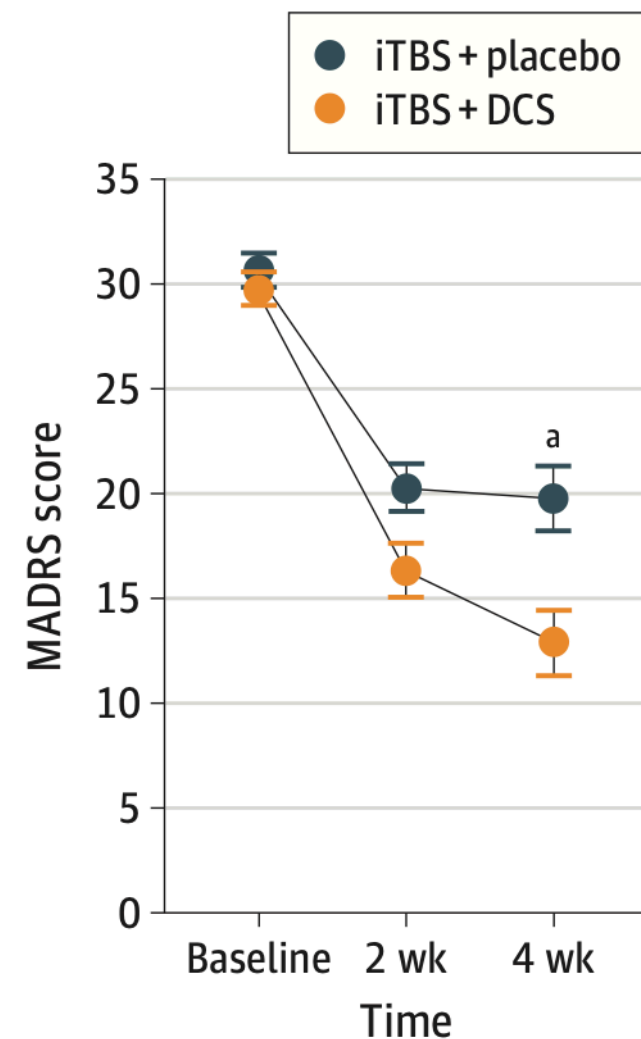
Key Points

Question Can the efficacy of transcranial magnetic stimulation in major depressive disorder be enhanced with a pharmacological adjunct?

Findings In this double-blind, placebo-controlled, randomized clinical trial that included 50 participants, those receiving intermittent theta-burst stimulation with adjunctive D-cycloserine (100 mg) had significantly greater improvements in depressive symptoms compared with stimulation with a placebo.

Meaning Adequately powered multisite studies are required to confirm whether adjunctive D-cycloserine enhances antidepressant treatment outcomes with intermittent theta-burst stimulation transcranial magnetic stimulation in major depressive disorder.

A MADRS score





Real-world effectiveness of a single-day regimen for transcranial magnetic stimulation using Optimized, Neuroplasticity-Enhanced techniques in Depression (ONE-D): An open-label case series

Donald A. Vaughn^a, Brooke Marino^{a,c}, Alex Engelbertson^c, Aleksandra Dojnov^a,
Lena Johnson^a, Madison Stine^c, Fidel Vila-Rodriguez^d, Nicholas Weiss^c, Georgine Nanos^b,
Jonathan Downar^{a,e,f,*}

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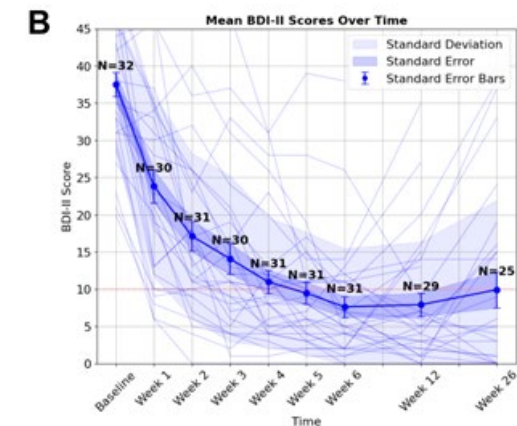
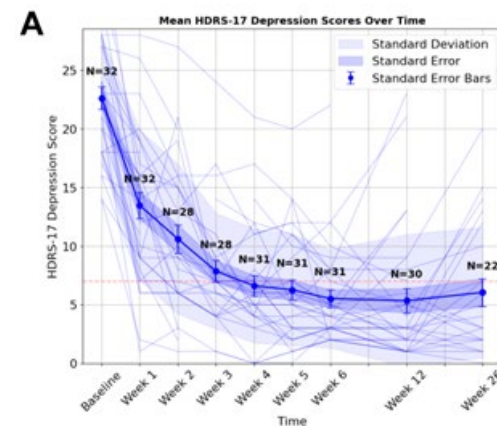
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The Foundation for the Advancement of Clinical TMS (FACTMS) celebrates the opening of the Neil S. Hirsch TMS Center at Kitsap Mental Health Services!

[Watch the Ribbon Cutting!](#)

The Foundation for the Advancement of Clinical TMS (FACTMS) is pleased to announce the opening of the first Neil S. Hirsch TMS Center at Kitsap Mental Health Services in Bremerton, Washington. Transcranial Magnetic Stimulation (TMS) is a cutting-edge treatment for depression and other neuropsychiatric disorders.

“As FACTMS President, I am honored to announce the opening of the first FACTMS sponsored Neil S. Hirsch TMS clinic in alliance with Kitsap Mental Health Services,” said Dr. Randy Pardell. “This represents a significant step forward in our mission to broaden access to transformative TMS therapy. Our partnership with the Neil S. Hirsch Foundation at Kitsap is a testament to our shared commitment to revolutionize psychiatric care and empower individuals facing neuropsychiatric disorders. Through this clinic, we honor Neil’s enduring legacy as a visionary and advocate, ensuring that his impact continues to uplift and transform lives.”

“As a mental health advocate, Neil would have been so proud to collaborate in the development of this clinic, bringing cutting-edge advances in neuromodulation to those who suffer with mental illness,” said Steven N. Rappaport, Trustee of the Neil S. Hirsch Foundation.

Ethical and Legal Considerations

Disclaimer: I am not an ethicist or legal expert!

Legal pathways have not kept pace with newer modalities

In involuntary settings, safeguards must prevent inappropriate treatment without making clinically indicated care unavailable

ECT

An established – though variable – legal pathway

- Court authorization and substituted-judgment processes are established in many jurisdictions.

- State standards vary and may turn on impaired capacity, risk of harm, or other compelling governmental interests.

Sell v. U.S. • Washington v. Harper

TMS + EMERGING NEUROMODULATION

Absence of a pathway can become a barrier

- Newer modalities (e.g., TMS, etc.) may be absent from statutes, case law, and institutional policy
- Uncertain whether these treatments can be used at all when consent capacity is impaired
- Different standards across settings (capacity, autonomy, perceived safety, etc.)

OVERSIGHT SHOULD TRACK THE INTERVENTION

Safety profiles and perceived intrusiveness differ across modalities. Each modality needs a clear route that protects against both inappropriate use and inappropriate exclusion.

Informed consent is a process – and a policy infrastructure

Clear information, careful capacity assessment, and consistent decision pathways are essential across voluntary and involuntary settings

A MEANINGFUL CONSENT PROCESS

1	Nature/purpose	What the treatment does and why it is being recommended
2	Benefits/risks	Common/serious adverse effects vs. expected benefit
3	Alternatives	Other treatments and the risks of no treatment
4	Understanding + capacity	Confirm comprehension and ability to make decision

WHEN CAPACITY IS IMPAIRED

Honor patient preferences whenever possible

- Healthcare proxy or legal representative
- Guardian applying best-interest standard
- Court oversight

POLICY PRIORITIES

- Standardize consent processes
- Clarify legal pathways for all modalities
- Protect rights through oversight/review
- Educate patients and families
- Preserve access across status/setting
- Train clinicians in capacity and consent

GUIDING PRINCIPLES

Beneficence

Provide effective care for life-threatening illness

Respect for autonomy

Use shared decision-making whenever possible

Least restrictive care

Match intrusiveness to clinical need

Access is ethical

Withholding effective care may also cause harm

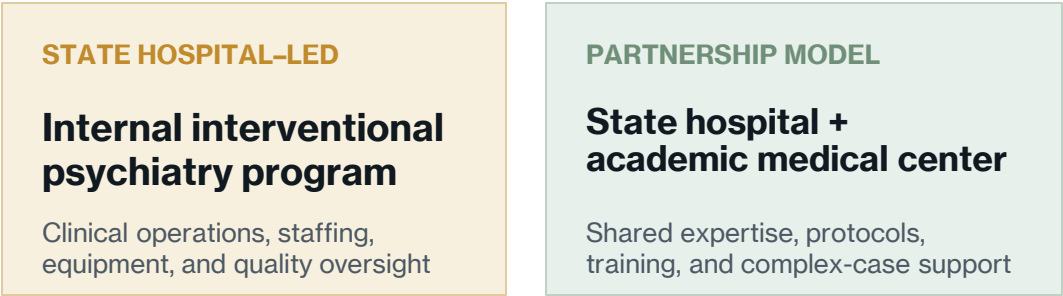
Implementation Considerations

Disclaimer: I am not a State Mental Health Program Director!

Two hub models can extend expertise across the public system

Goal: concentrate expertise while extending referral, training, and continuation care across the public system

TWO VIABLE HUB MODELS



SHARED CARE PATHWAY



Infrastructure must fit the modality

ECT Procedural suite • anesthesia • recovery and monitoring • ongoing quality oversight

TMS Dedicated treatment rooms • equipment and staffing • scheduling capacity for repeated or accelerated courses

EMERGING Imaging integration, surgical capacity, or specialized monitoring – depending on the intervention

DESIGN AROUND THE FULL EPISODE Co-location and structured transitions improve access and continuity.

Scaling clinical capacity and payment policy together

Expanding equipment without a trained team – or training a team without a viable payment pathway – does not create durable access.

WORKFORCE

Build a team, not just a procedural skill

Psychiatrists Residency exposure • fellowships or certification • continuing education • patient selection, safety, ethics, and longitudinal care

TMS Techs, RNs Evaluation, screening, aspects of TMS delivery, monitoring, and follow-up – within state law and institutional policy

Referral network Educate referring clinicians and reduce stigma so eligible patients reach treatment earlier.

FINANCING

Pay for the course of care – not just the procedure

Close coverage gaps Reduce interstate variability in TMS and ECT coverage, site-of-service restrictions, and exclusions of newer protocols.

Modernize payment Consider accelerated and targeted approaches, as well as bundled or episode-based payment for a complete treatment course.

Evaluate total system impact Evaluate equipment and staffing alongside potential reductions in hospitalization, emergency care, and prolonged illness.

STATE ACTION **Align capital investment, workforce development, Medicaid policy, and quality oversight around a regional service model.**

Policy Recommendations

I zoned out – what is the take home message?

A durable state-level strategy requires coordinated policies

Coverage alone cannot create access; policy must also build delivery capacity and a learning system.

ACCESS Help patients reach treatment earlier	1 Expand Medicaid coverage Cover evidence-based ECT and TMS consistently; reduce step therapy that delays indicated care.	2 Integrate settings Connect community, emergency, inpatient, crisis, step-down, maintenance, and follow-up care.	3 Modernize reimbursement Create viable pathways for accelerated, targeted, bundled, or episode-based care as evidence supports them.
DELIVERY CAPACITY Build a system capable of delivering care	4 Develop regional centers Create hubs for high-acuity care, referral, consultation, training, quality improvement, and telehealth support.	5 Invest in the workforce Support residency, fellowship or certification, advanced practice roles, and referral education.	6 Address capital barriers Fund equipment and facilities; support co-location and shared or regional resource models.
ACCOUNTABILITY Make expansion measurable and improvable	7 Build a learning system Standardize outcomes and reporting across sites. Track utilization, outcomes, function, and cost. Support QI.	ACADEMIC PARTNERSHIPS Support analysis and learning without replacing public-system autonomy	



CONCLUSION

The pyramid attracts attention, but access is the real impact.

EVIDENCE

Brain circuit therapeutics can improve outcomes and potentially save money in severe, treatment-resistant illness.

PATHWAYS

Regional referral and delivery networks connect patients to specialized care.

FOUNDATIONS

Workforce, financing, legal clarity, continuity, and outcomes monitoring make access sustainable.