Northwest (HHS Region 10)
ATTC Addiction Technology Transfer Center Network
Funded by Substance Abuse and Mental Health Services Administration

The Northwest & Pacific Southwest ATTCs and the CTN Western States Node present:

CTN-0108: Transcranial Magnetic Stimulation in the Treatment of Stimulant Use Disorder

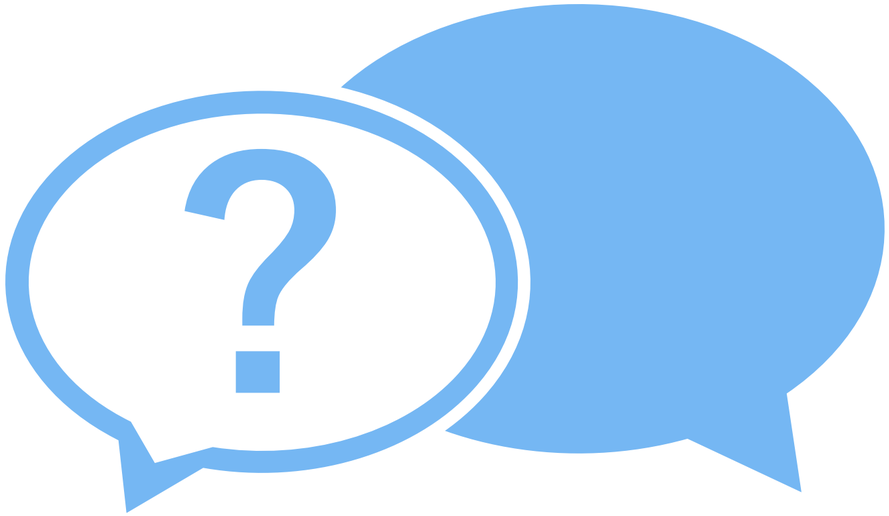
Thank you for joining us! The webinar will begin shortly.

- **You are muted with camera off.** Attendees are automatically muted with their cameras off for the webinar. **Please type questions in the chat box!**
- **This webinar is being recorded** and will be made available on our website tomorrow at attcnetwork.org/northwest

SAMHSA
Substance Abuse and Mental Health Services Administration

Q&A

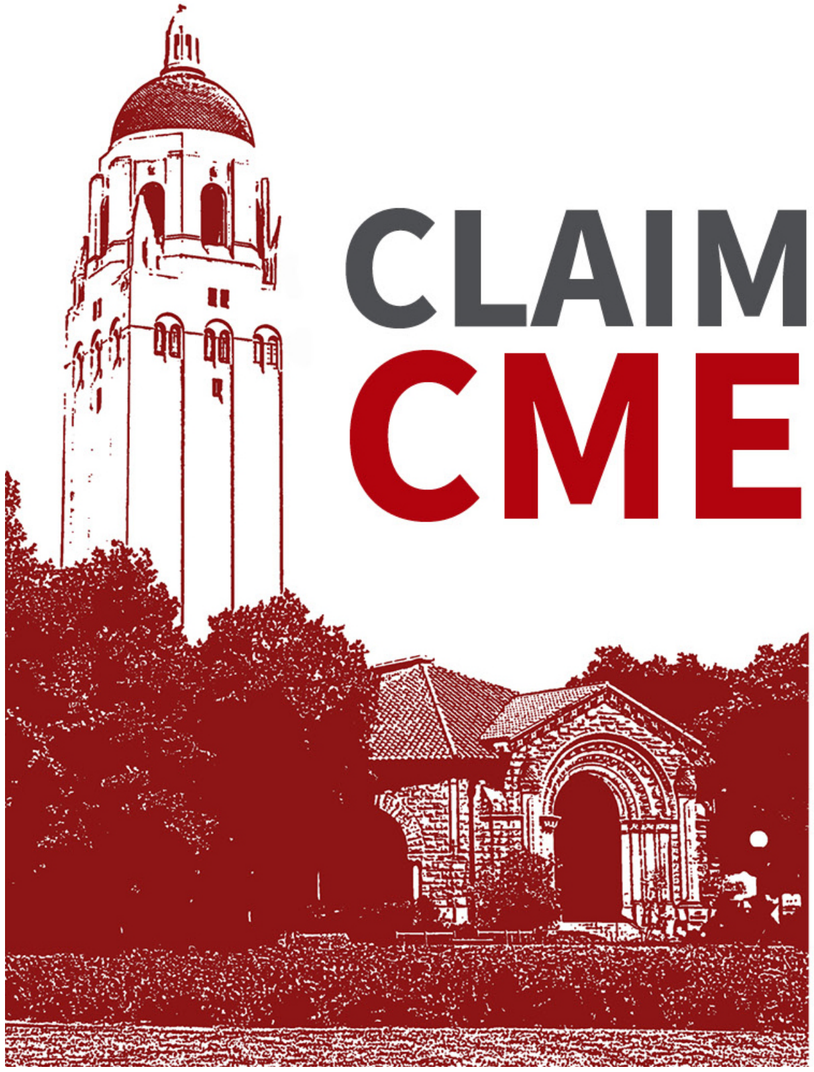
Questions? Please type them in the chat box!



ATTC Survey, Slides, Recording

Look for our survey in your inbox!

We greatly appreciate your feedback! Every survey we receive helps us improve and continue offering our programs.



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All of the relevant financial relationships listed for these individuals have been mitigated.

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- Following the web training, LMFTs, LCSWs, and SUD counselors will receive an email from **Brandy Oeser** with the links to two different brief online CE course evaluations.
- Once you submit your CE evaluation form, a CE Certificate will be emailed to you within **6-8 weeks**

- Reach out to **Brandy** with questions (BOeser@mednet.ucla.edu)

Certificate of Attendance

If you requested a “certificate of attendance” rather than specific CME/CE, you will receive that certificate from the Northwest ATTC automatically via email within a week.

NORTHWEST ATTC

SEVEN DIRECTIONS
A CENTER FOR INDIGENOUS PUBLIC HEALTH

Webinar: July 30, 2025; 12-1pm PT

Incorporating Indigenous Evaluation into a Tribal Clinical Supervision Learning Collaborative

A panel presentation and community of practice led by Danielle Eakins, PhD; Paul Hunziker, MA,LMFT, SUDP; and Lynsey Parrish, LICSW

Neuromodulation for Stimulant Use Disorders

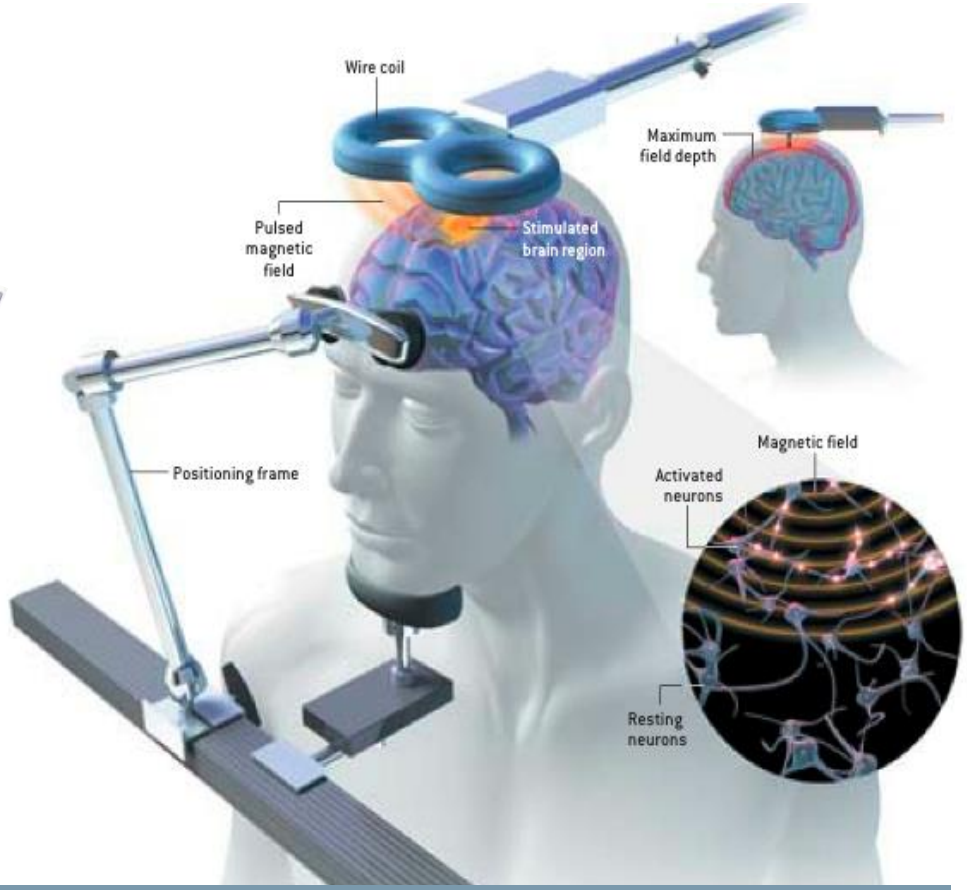
Kathleen Brady, MD, PhD

Co-PI, CTN Southern Consortium Node

MUSC Medical University of South Carolina

South Carolina Clinical & Translational Research Institute

WHAT IS TMS?

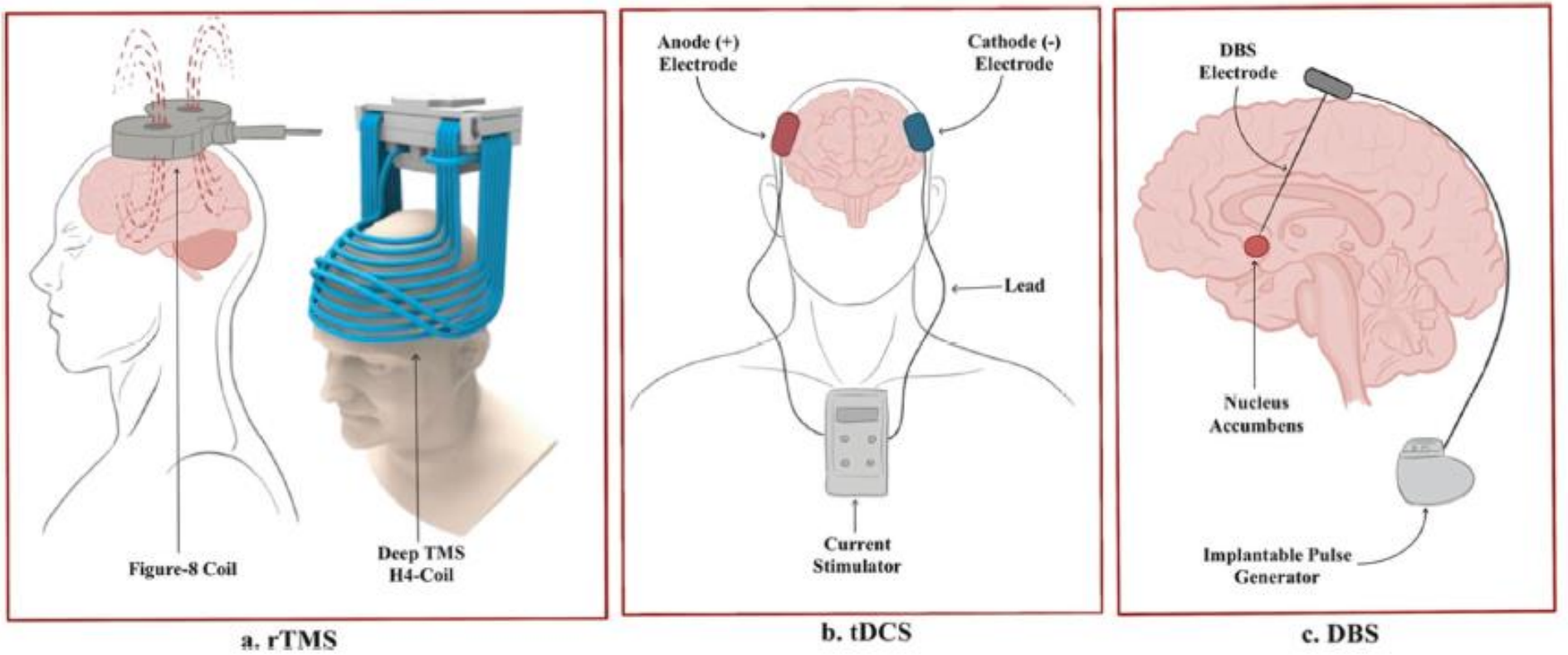


George MS. *Sci Am.* 2003;289:66-73.

TRANSCRANIAL MAGNETIC STIMULATION

Non-invasive form of brain stimulation - changing magnetic field is used to cause electric current in specific brain regions through electromagnetic induction

Neuromodulation Techniques



rTMS (Repetitive Transcranial Magnetic Stimulation)

How it works: Delivers repeated magnetic pulses to a targeted brain region at a steady frequency.

Frequency: Can be low-frequency (around 1 Hz, usually inhibitory) or high-frequency (5-20 Hz, usually excitatory).

Duration: Sessions typically last 20-40 minutes or more.

Pulse pattern: Continuous, repetitive pulses.

Purpose: Often used to modulate cortical excitability by either increasing or decreasing brain activity.

Clinical Use: FDA-cleared for depression, OCD, migraine, smoking cessation

Theta Burst

iTBS (Intermittent Theta Burst Stimulation)

How it works: A specific patterned form of TMS that mimics the natural theta brain wave rhythms (around 5 Hz)

Pulse pattern: Bursts of 3 pulses at 50 Hz, repeated at 5 Hz intervals (theta rhythm), delivered in short bursts (2 seconds on, 8 seconds off)

Duration: Short sessions - usually only 3-4 minutes per session

Effect: Generally excitatory, enhancing cortical activity

Efficiency: Achieves similar or better effects as high-frequency rTMS but with shorter treatment times

Clinical Use: Also FDA-approved for depression; gaining popularity because of efficiency and tolerability

Comparison of rTMS and iTBS

Feature	rTMS	iTBS
Stimulation Pattern	Continuous pulses at fixed frequency	Bursts of pulses mimicking theta rhythm
Frequency	Low or high (1-20 Hz)	50 Hz bursts repeated at 5 Hz
Session Duration	20-40 minutes or longer	~3-4 minutes
Effect	Can be excitatory or inhibitory	Mostly excitatory
Efficiency	Longer sessions	Shorter, time-efficient
Clinical Use	Depression, OCD, migraines Smoking cessation	Depression (FDA-approved)

Accelerated rTMS Protocols

Definition: Multiple rTMS sessions delivered in one day (3-10+), usually spaced out by short intervals

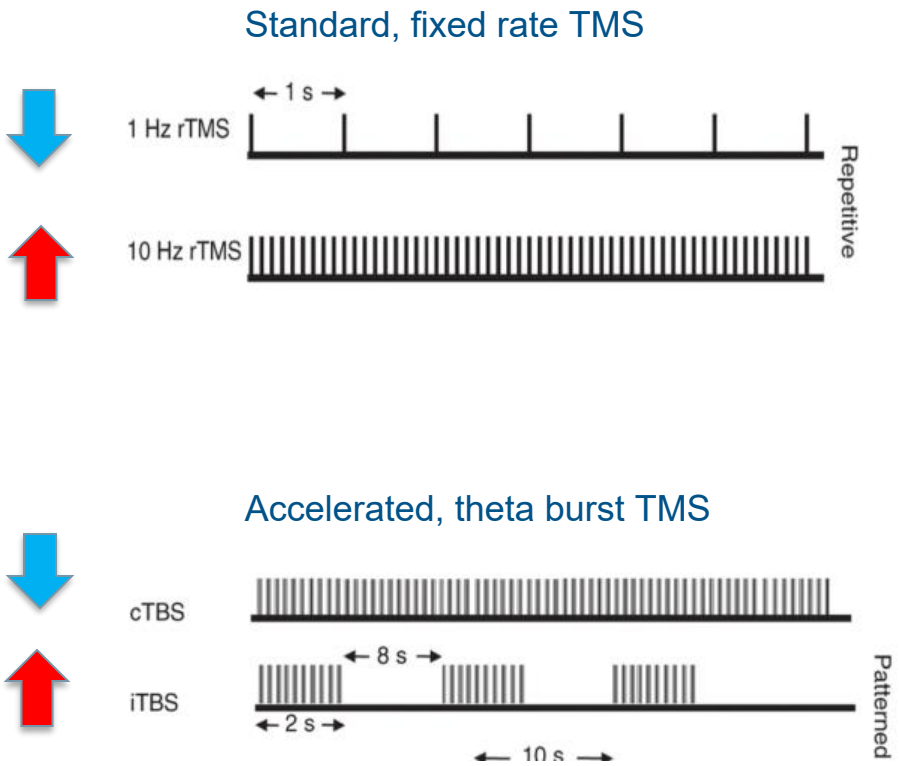
Goal: Achieve faster symptom relief, completed in days-weeks rather than months. Particular advantage in populations where retention in treatment is an issue

Rationale: Neuroplastic changes induced by rTMS may be enhanced or accumulated more rapidly by increasing session frequency

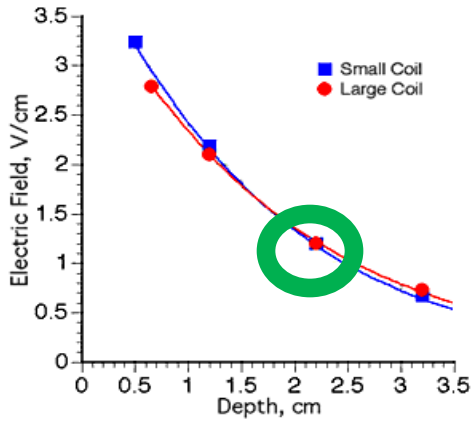
Risk-benefit: Less experience with technique, so more careful safety monitoring

Behavioral and Brain effects are frequency dependent

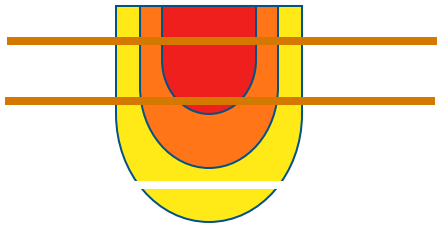
Frequency dependent modulation of cortical targets		
High Frequency (10Hz) Intermittent Theta Burst	higher cortical excitability	Amplified neural response
Low Frequency (1Hz) Continuous Theta Burst	lower cortical excitability	Attenuated neural response

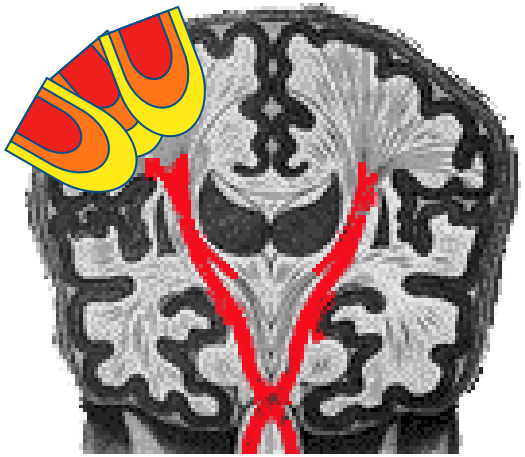


TMS Principles : Stimulation Depth



1 V/cm = 20mm deep, approx. 20mm wide



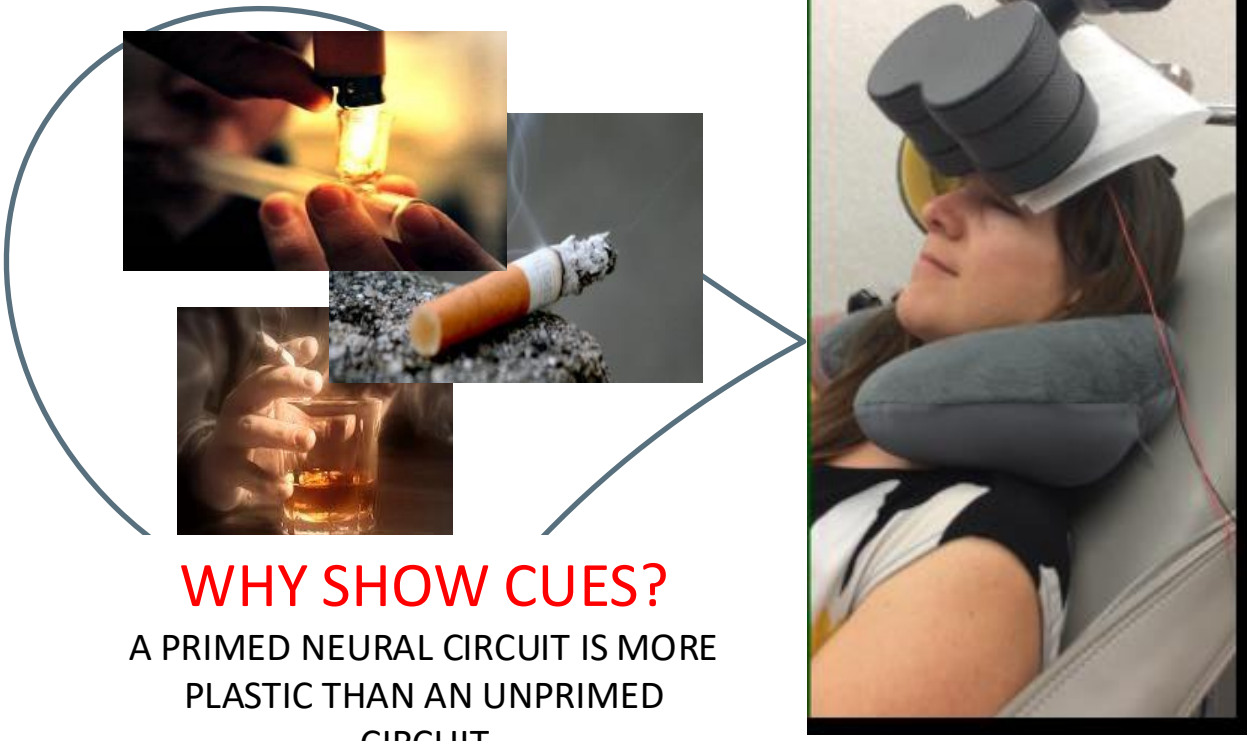


0.5 cm

1.5 cm

2.0 cm

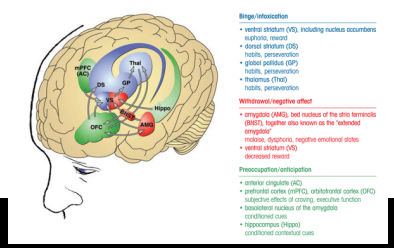
Important Methods Issues:
What Task is the Person Doing Before/During TMS?

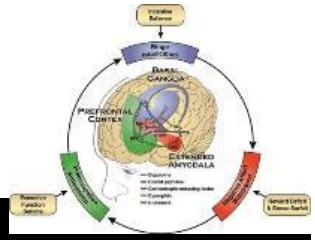


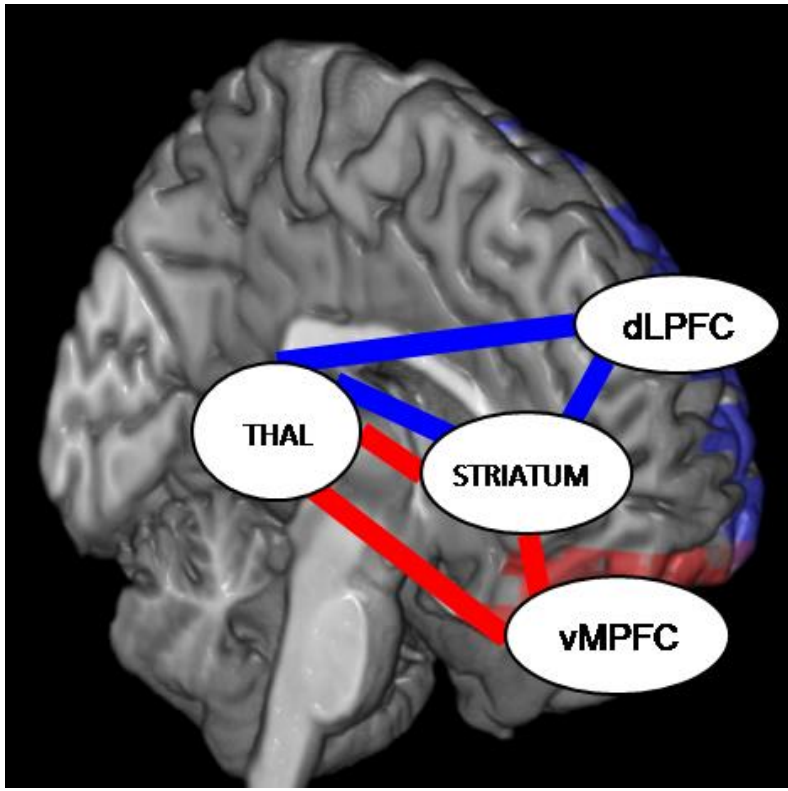
WHY SHOW CUES?

A PRIMED NEURAL CIRCUIT IS MORE PLASTIC THAN AN UNPRIMED CIRCUIT

Theoretical Constructs for Treating Cue-induced craving w/ TMS

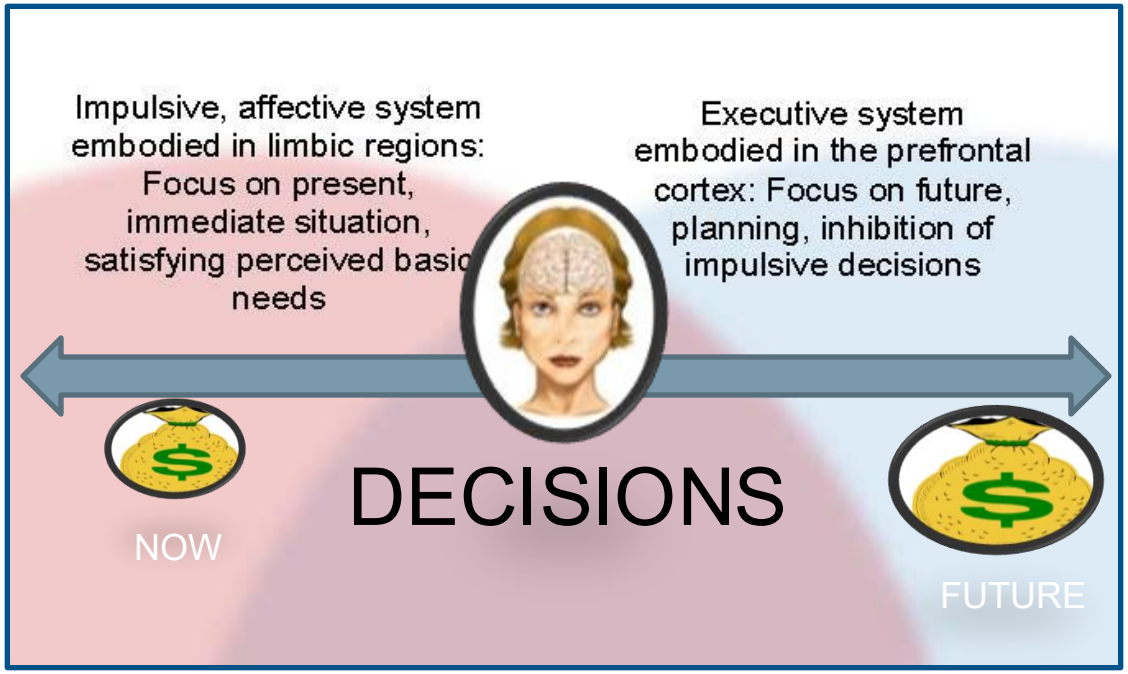






Approach		Example	
↑	Executive Control Loop	LTP-like stimulation	10–20 Hz iTBS
↓	Limbic Arousal Loop	LTD-like stimulation	1-5Hz cTBS

Competing Neurobehavioral Decisions Systems Model



13. Bickel, W. K., M. L. Miller, et al. (2007). "Behavioral and neuroeconomics of drug addiction: competing neural systems and temporal discounting processes." Drug and Alcohol Dependence 90 Suppl 1: S85-91.

TMS in Depression - Approved in 2008

Still questions:

? Where to stimulate

? Accelerated treatment – multiple treatments in 1 day, more rapid response

? Brain state at time of procedure

? Refining frequencies and patterns – Theta burst

? Durability, maintenance

Sheffer: rTMS in Tobacco Use Disorder

Review:

2 dozen studies

Mostly positive, mixed

Methodologic inconsistencies

Data from well-controlled study with use outcomes promising

Dosing study in progress

Questions combination therapy

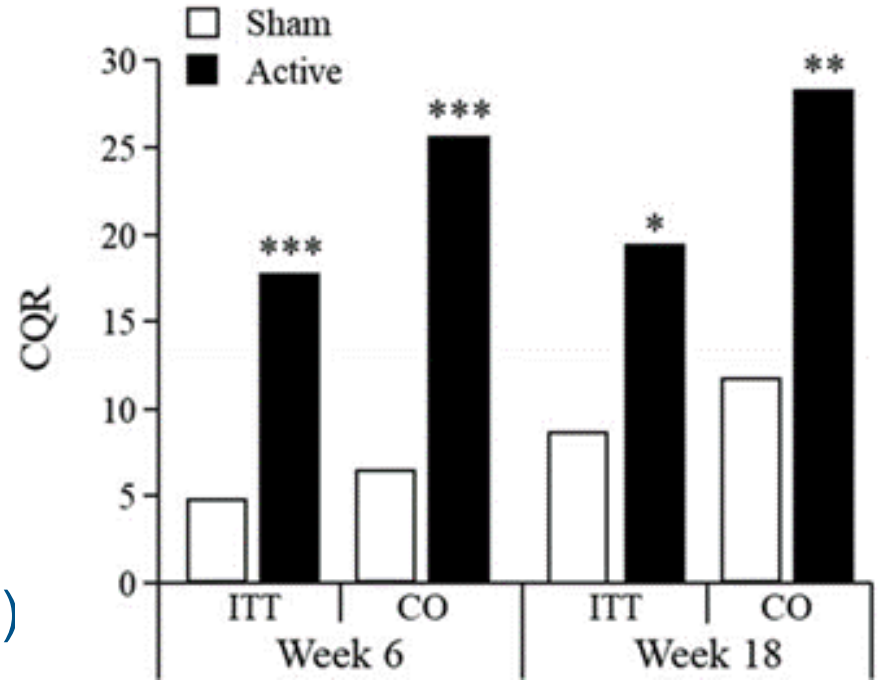
Repetitive transcranial magnetic stimulation for smoking cessation: Pivotal multicenter double-blind randomized controlled trial (Zangen et al, World Psychiatry, 2021)

Randomized, double-blind multi-center trial

262 subjects, sham-controlled

3 wk daily trt; 3 wk follow-up

Primary outcome:
4 wk Continuous Quit Rate (CQR)



FDA-cleared short-term smoking cessation

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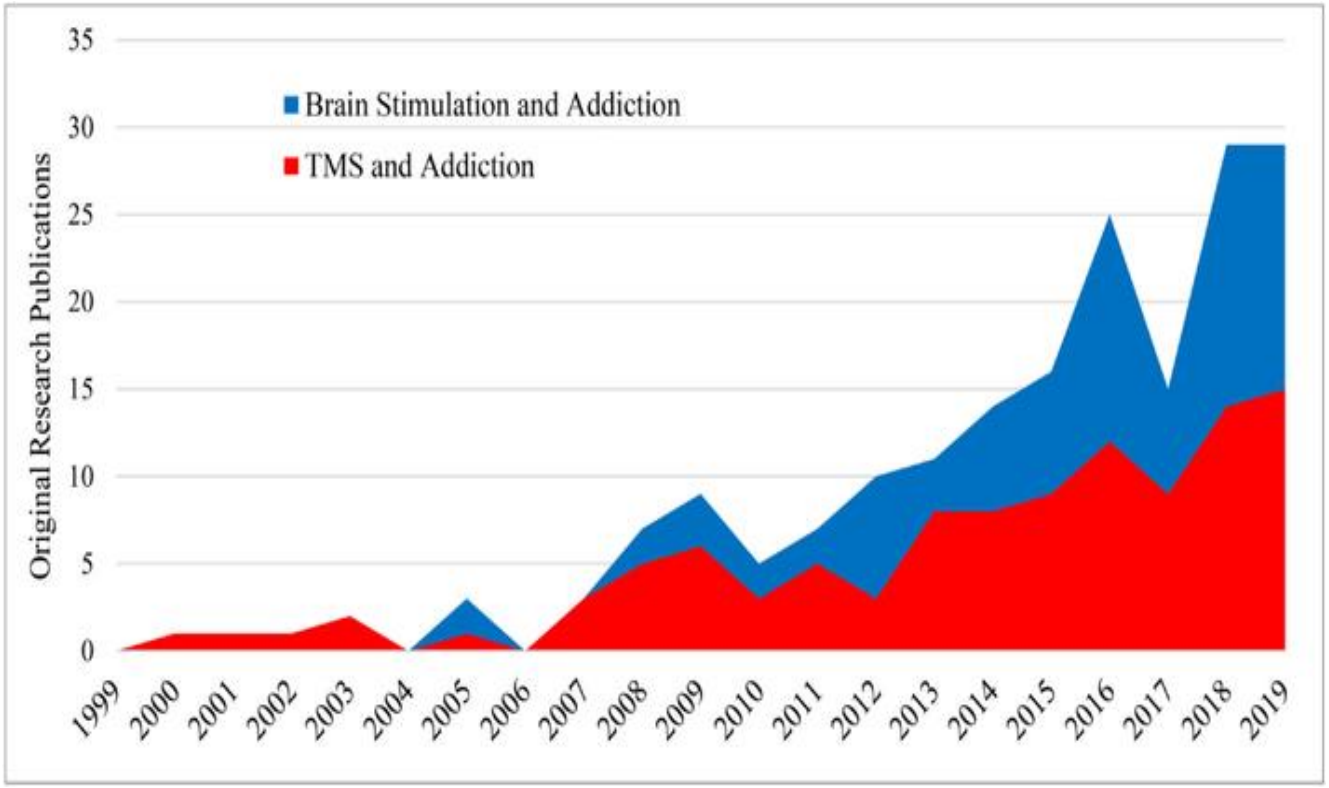
STUDIES FOCUSED ON BRAIN STIMULATION AND ADDICTION



FDA-cleared for treatment of depression and short term facilitation of smoking cessation

Mahoney et al.,
J Neurol Sci. 2021 Nov 15; 418

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Included Studies/Protocols Stratified According to the Type of Brain Stimulation and Substance

Condition	TMS	tDCS	tACS	DBS	VNS	Multiple	Total	%
Alcohol	23	19	1	6	1	–	50	30.7
Opioid	14	5	–	10	1	1[a]	31	19.0
Nicotine	20	8	–	–	–	–	28	17.2
Cocaine	12	5	–	1	–	–	18	11.0
Cannabis	13	4	–	–	–	–	17	10.4
Any stimulant[b]	12	1	–	1	–	–	14	8.6
Multiple	2[c,d]	2[e,f]	–	–	–	1[g]	5	3.1
Total	96	44	1	18	2	2	163	100.0
%	58.9	27.0	0.6	11.0	1.2	1.2	100.0	-

TMS, transcranial magnetic stimulation; tDCS, transcranial direct-current stimulation; tACS, transcranial alternating current stimulation; DBS, deep brain stimulation; VNS, vagus nerve stimulation.

[a]TMS, tDCS.

[b]Includes 10 studies focused only on amphetamine/methamphetamine.

[c]Alcohol, opioid, cocaine.

[d]Alcohol, cocaine.

[e]Any substance (not limited to specific few).

[f]Alcohol, stimulants.

[g]Nicotine, opioid: DBS, tDCS.

Included Studies/Protocols Stratified According to the Type of Brain Stimulation and Their Neuroanatomical Target

Targets	TMS	tDCS	DBS	multiple	VNS	Total	%
dlPFC	62	28	–	–	–	90	53.6
mPFC	18	1	–	–	–	19	11.3
PFC	5	5	–	1[a]	–	11	6.5
NAc	1	–	15	1[b]	–	17	10.1
aIC	–	–	6	–	–	6	3.6
Insula	4	–	–	1[b]	–	5	3.0
ACC	4	–	–	1[b]	–	5	3.0
Cerebellum	1	1	–	–	–	2	1.2
Motor cortex	2	–	–	–	–	2	1.2
Parietal cortex	1	1	–	–	–	2	1.2
Transcutaneous[c]	–	–	–	–	2	2	1.2
Inf frontal gyrus	1	–	–	–	–	1	0.6
Sup frontal gyrus	1	–	–	–	–	1	0.6
OFC	1	–	–	–	–	1	0.6
STN	–	–	1	–	–	1	0.6
TPJ	–	1	–	–	–	1	0.6
Limbic pallidum	–	–	1	–	–	1	0.6
vStriatum	–	–	1	–	–	1	0.6
Total	101	37	24	4	2	168[d]	100

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Brain Stimulation in Addiction

(Sailing and Martinez, Neuropsychopharm 2016)

"an acute effect on craving for drugs and alcohol… few studies investigating relapse or use"

Various regions stimulated

Mechanism not well understood

Great potential – further investigation needed

Table 1 Transcranial Magnetic Stimulation (TMS)

Drug	Treatments	*n*	Target	Stimulation	Outcome measures	Effect	Citation
Nicotine	1	11	L DLPFC	10,20 Hz, 90,100% MT	Craving	↓	Johann *et al*, 2003
	1	16	L DLPFC	10 Hz, 100% MT	Cue-induced craving	↓	Li *et al*, 2013a, b
	2	14	L DLPFC	20 Hz, 90% MT	Craving Ad libitum smoking	No effect ↓	Eichhammer *et al*, 2003
	1	14	L DLPFC	10 Hz, 90% MT	Cue-induced craving EEG delta	↓ ↓	Pripfl *et al*, 2014
	1	10	L DLPFC	1 Hz, 110% MT	Cue-induced craving fMRI: ACC, OFC, VS	↓ ↓	Hayashi *et al*, 2013
	1	15	SFG SFG MOC	1 Hz, 90% MT 10 Hz, 90% MT 1, 10 Hz, 90% MT	Cue-induced craving Cue-induced craving Cue-induced craving	No effect ↓ No effect	Rose *et al*, 2011
	10	48	L DLPFC	10 Hz, 100% MT	Cue-induced craving Cigarette consumption	↓ ↓	Amiaz *et al*, 2009
	20, w therapy	15	L,R DLPFC	20 Hz, 90% MT	Craving Smoking	↓ No effect	Wing *et al*, 2012
	15	35	L DLPFC	10 Hz, 110% MT	Smoking	↓	Prikryl *et al*, 2014
	13, h-coil, w/cues	115	PFC, insula PFC, insula	1 Hz, 120% MT 10 Hz, 120% MT	Cigarette consumption Cigarette consumption	No effect ↓	Dinur-Klein *et al*, 2014
Alcohol	10	45	R DLPFC	10, Hz, 110% MT	Craving	↓	Mishra *et al*, 2010
	10	20	R and L DLPFC	10, Hz, 110% MT	Craving	↓	Mishra *et al*, 2015
	1	31	R DLPFC	20 Hz, 110% MT	Craving (lab) Craving (home)	No effect No effect	Herremans *et al*, 2012
	1	29	R DLPFC	20 Hz, 110% MT	Craving Response inhibition	No effect ↑	Herremans *et al*, 2013
	1	19	L DLPFC	20 Hz, 90% MT	Craving Depressive symptoms Alcohol cue attention	No effect No effect ↓	Hoppner *et al*, 2011
	20, h-coil	11	MPFC LPFC	20 Hz, 120% MT	Craving	↓	Rapinesi *et al*, 2015
	10	18	MPFC	20 Hz, 120% MT	Craving Depressive symptoms	↓ ↓	Ceccanti *et al*, 2015
Cocaine	1	6	R DLPFC	10 Hz, 90% MT	Craving	↓	Camprodon *et al*, 2007
		6	L DLPFC	10 Hz, 90% MT	Craving	No effect	
	10	36	L DLPFC	15 Hz, 100% MT	Craving	↓	Politi *et al*, 2008
	1	11	MPFC	cTBS, 110% MT	Craving	↓	Hanlon *et al*, 2015a, b
Methamph.	1	10	L DLPFC	1 Hz, 100% MT	Craving	↑	Li *et al*, 2013a, b

Abbreviations: L, left; R, right; cTBS, theta burst simulation; DLPFC, dorsolateral prefrontal cortex; MOC, motor cortex; MT, motor threshold; MPFC, medial prefrontal cortex; PFC, prefrontal cortex; SFG, superior frontal gyrus; VS, ventral striatum.

Repetitive Transcranial Magnetic Stimulation in Patients With MUD: A Systematic Review and Meta-Analysis (Chang et al., 2022)

OVERALL EFFICACY

Double-blind, randomized, sham-controlled trials of TMS for SUD

7 trials; 462 participants

Evaluated craving, not use

Suggestion that iTBS superior to 10 HZ TMS

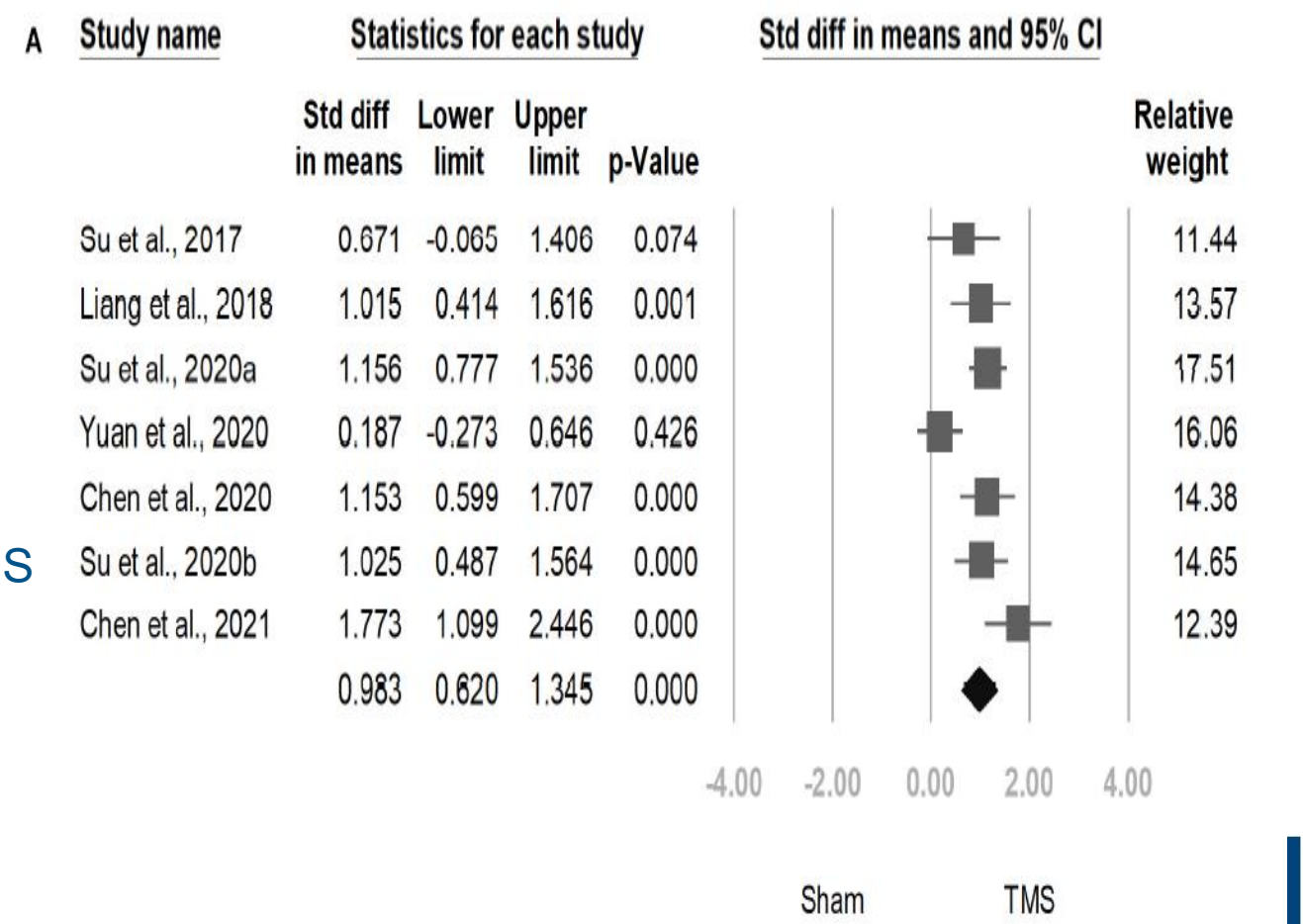


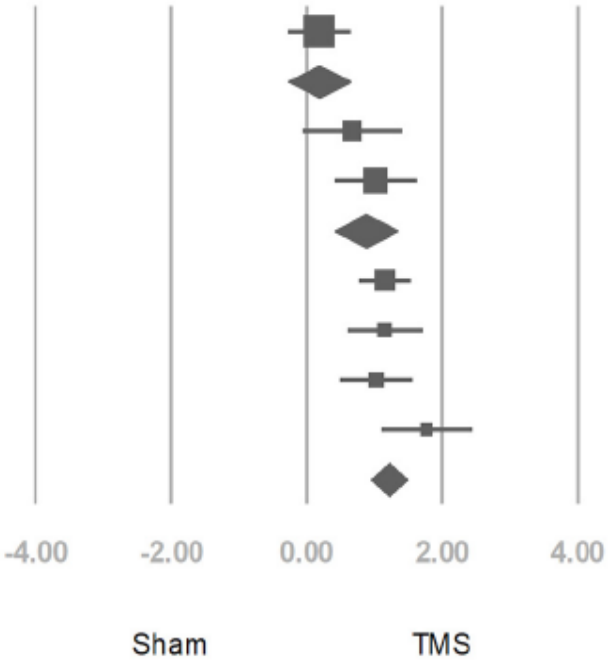
Figure adapted from Chang et al. (2022), licensed under CC BY 4.0.

rTMS and MUD: Review and Meta-Analysis

Stimulation Frequency

B

Group by Frequency	Study name	Std diff in means	Lower limit	Upper limit	p-Value	Relative weight
1 Hz	Yuan et al., 2020	0.187	-0.273	0.646	0.426	100.00
1 Hz		0.187	-0.273	0.646	0.426	
10 Hz	Su et al., 2017	0.671	-0.065	1.406	0.074	40.04
10 Hz	Liang et al., 2018	1.015	0.414	1.616	0.001	59.96
10 Hz		0.877	0.412	1.342	0.000	
iTBS	Su et al., 2020a	1.156	0.777	1.536	0.000	41.86
iTBS	Chen et al., 2020	1.153	0.599	1.707	0.000	21.18
iTBS	Su et al., 2020b	1.025	0.487	1.564	0.000	22.32
iTBS	Chen et al., 2021	1.773	1.099	2.446	0.000	14.65
iTBS		1.217	0.953	1.481	0.000	



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rTMS and MUD: Review and Meta-Analysis

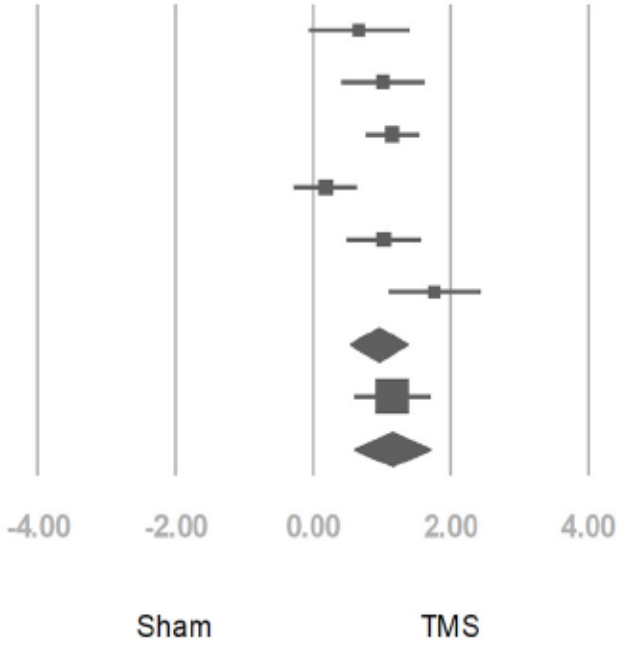
Brain Region

C

Group by Brain target	Study name	Std diff in means	Lower limit	Upper limit	p-Value	Relative weight
Left DLPFC	Su et al., 2017	0.671	-0.065	1.406	0.074	13.77
Left DLPFC	Liang et al., 2018	1.015	0.414	1.616	0.001	15.99
Left DLPFC	Su et al., 2020a	1.156	0.777	1.536	0.000	19.89
Left DLPFC	Yuan et al., 2020	0.187	-0.273	0.646	0.426	18.49
Left DLPFC	Su et al., 2020b	1.025	0.487	1.564	0.000	17.10
Left DLPFC	Chen et al., 2021	1.773	1.099	2.446	0.000	14.77
Left DLPFC		0.956	0.535	1.378	0.000	
vmPFC Left DLPFC	Chen et al., 2020	1.153	0.599	1.707	0.000	100.00
vmPFC Left DLPFC		1.153	0.599	1.707	0.000	

Statistics for each study

Std diff in means and 95% CI



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Repetitive transcranial magnetic stimulation treatment for female methamphetamine use disorder

Liu et al. 2019

90 MUD women

Treatment as usual (TAU) vs TAU plus
rTMS

10 Hz DLPFC

#20 Treatments over 4 weeks

Primary outcome: Craving

Measured pre, end of trt and 60 days post

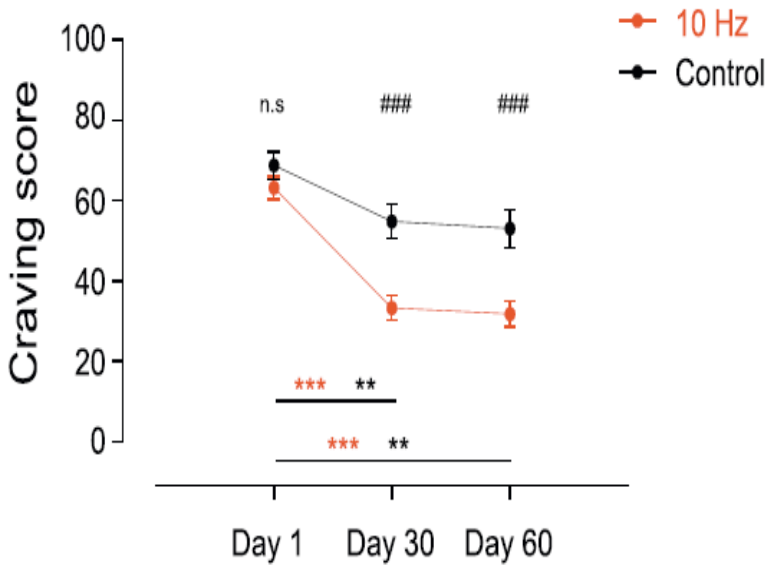


Fig. 3. The effect of rTMS in 10 Hz and control group. Inter group difference (# for $p < .05$, ## for $p < .01$ and ### for $p < .001$), and intra group difference (* for $p < .05$, ** for $p < .01$ and *** for $p < .001$) were showed. There were significant differences between 10 Hz group and control group at day 30/60 after the treatment ($p < .001$). The effect of time was also significant ($p < .001$) in the two groups.

Targeting Withdrawal Symptoms in MUD: Randomized Clinical Trial

Liang et al., 2018

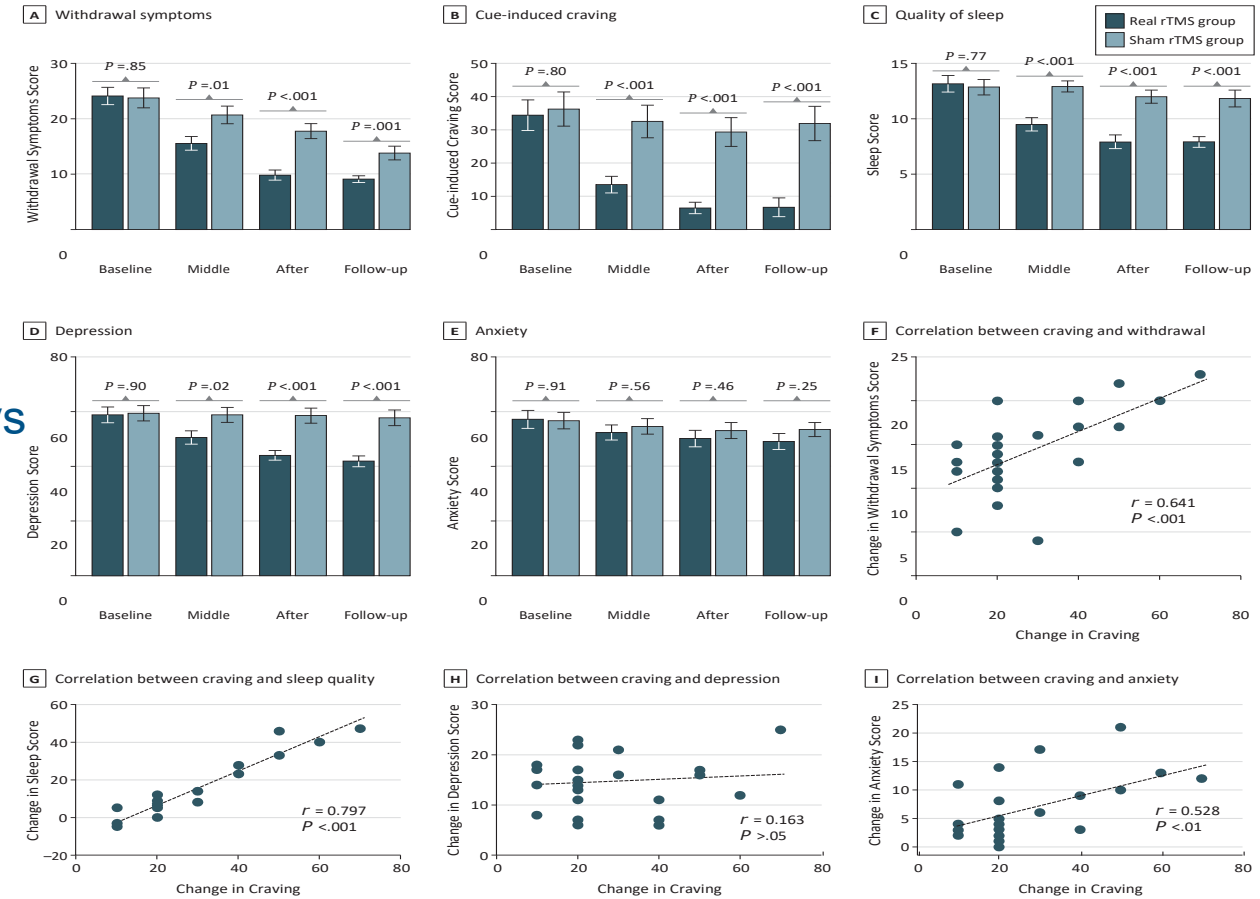
50 men with MUD

Sham-controlled

10 Hz trt L DLPFC

10 treatments over 12 days

Figure 2. Repetitive Transcranial Magnetic Stimulation (rTMS) Intervention Effects on Withdrawal Symptoms, Craving, Quality of Sleep, and Depression and Anxiety Scores



A, Withdrawal symptoms showed a significant difference for time ($F_{3,32}$ = 198.18; P < .001; $\eta p2$ = 0.81) and for a time × group interaction effect ($F_{3,}$ P < .001; $\eta p2$ = 0.31). Post hoc t tests (with Bonferroni correction for multiple comparisons) showed that withdrawal symptoms were significantly reduced for both the real rTMS group (t_{23} = 13.21; P < .001) and the sham rTMS group (t_{21} = 9.53, P < .001). B, Cue-induced craving showed a significant difference for time ($F_{3,132}$ = 50.52; P < .001; $\eta p2$ = 0.53) and for a time × group interaction effect ($F_{3,132}$ = 22.93; P < .001; $\eta p2$ = 0.34). Post hoc t tests (with Bonferroni correction for multiple comparisons) showed that the craving score was significantly reduced for the real rTMS group (t_{23} = 8.59; P < .001) but not for the sham rTMS group (t_{21} = 2.40; P = .046) after applying Bonferroni correction for multiple comparisons. C, Quality of sleep showed a significant difference for time ($F_{3,132}$ = 32.76;

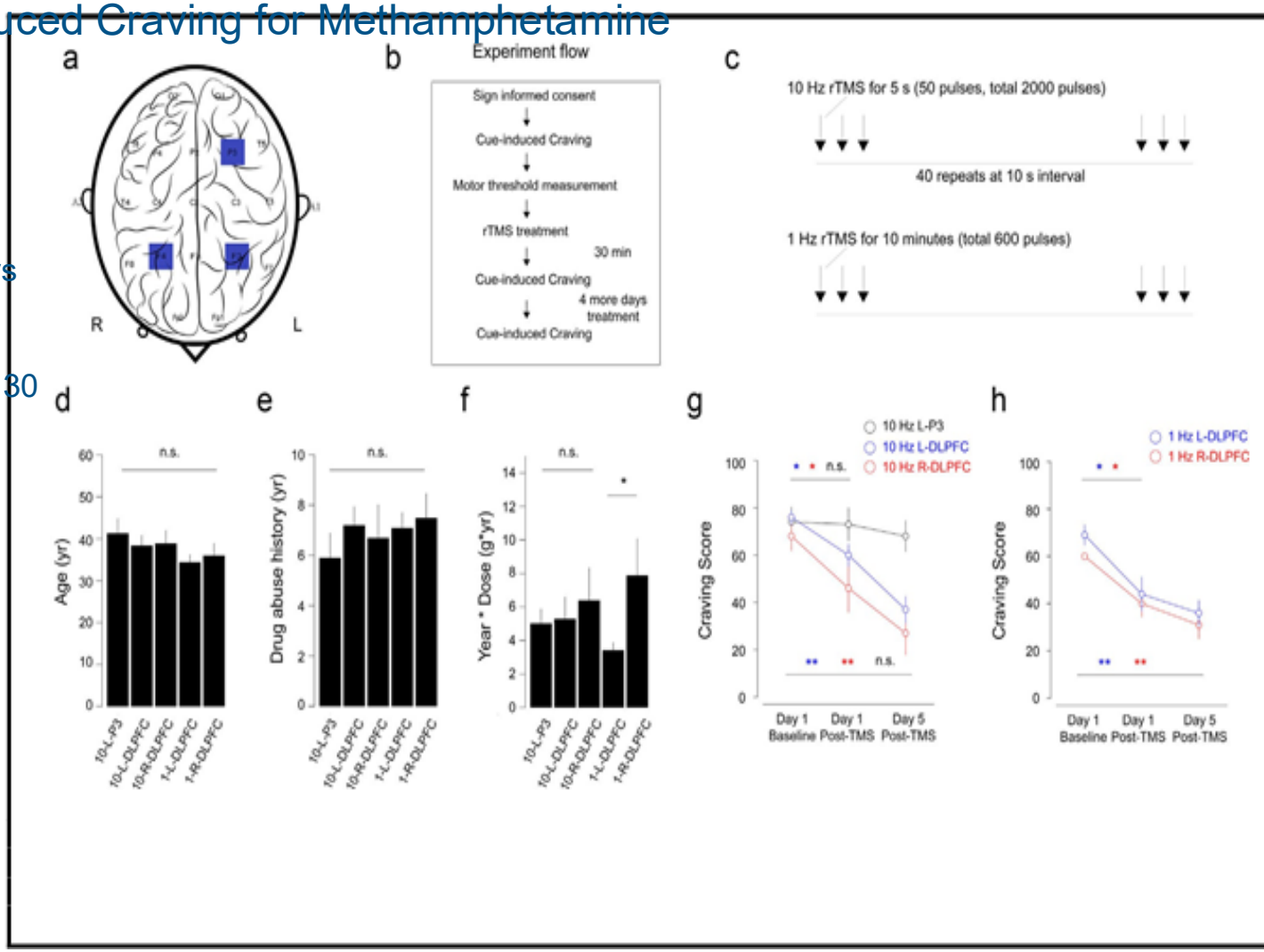
Either Left or Right, Both High and Low Frequency rTMS of Dorsolateral Prefrontal Cortex Decreases Cue Induced Craving for Methamphetamine

(Lui et al., 2017)

50 males with MUD

Daily treatment for 5 days

Craving measured immediately before and 30 min after treatment



rTMS to DLPFC reduces drug craving and improves decision-making ability in MUD: Controlled clinical trial

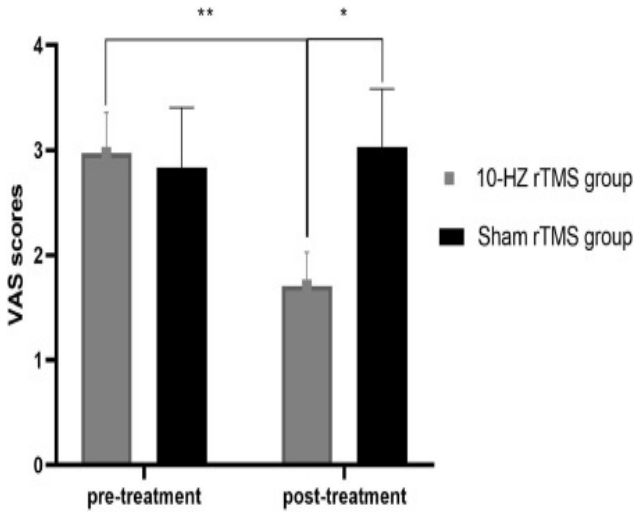
(Wang et al. 2022)

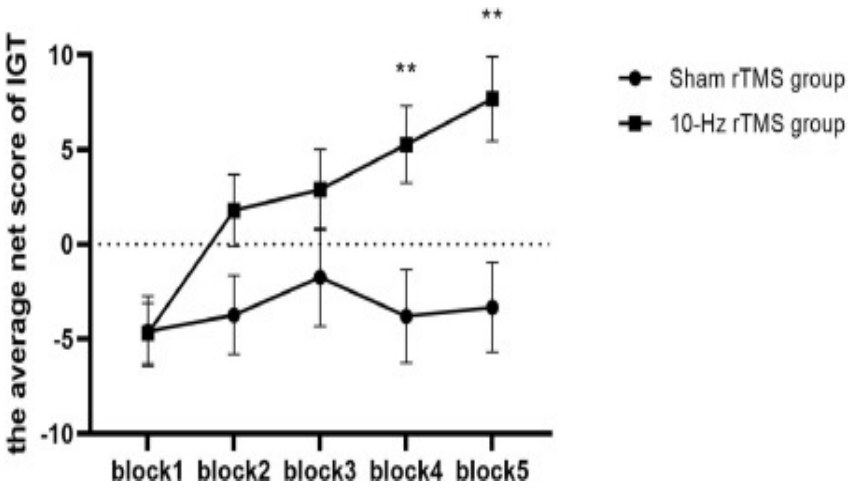
64 participants

10 HZ rTMS vs sham

Craving measured

Iowa Gambling Task: measures impulsivity





Wang et al., 2022
Psychiatry Research
Volume 317, November 2022, 114904

Modulating Neural Circuits with Transcranial Magnetic Stimulation: Stimulant Use Dx

Hanlon et al., Pharmacol Review, 2018

TABLE 3

Studies that have used repetitive TMS as a tool to cocaine or methamphetamine craving

This study performed 10 Hz TMS on the superior frontal gyrus and found an increase in craving but did not find a decrease in craving with 1 Hz to the superior frontal gyrus (L, left; R, right).

Author	Drug of Abuse	Sample Size	Site of TMS	Frequency	Sessions	Behavioral Effect?	Active Sham Control
Camprodon et al. (2007)	Cocaine	6	L/R DLPFC	10 Hz	1	Yes	Within subject
Hanlon et al. (2015b)	Cocaine	11	L vMPFC	cTBS	6[a]	Yes	Within subject
Hanlon et al. (2017)	Cocaine	25	L MPFC	cTBS	6[a]	Yes	Within subject
Politi et al. (2008)	Cocaine	36	L DLPFC	15 Hz	10	Yes	No
Rapinesi et al. (2016)	Cocaine	7	L DLPFC[b]	20 Hz	12	Yes	Between groups
Bolloni et al. (2016)	Cocaine	10	Bilat PFC/Ins[b]	10 Hz	12	No	Between groups
Terraneo et al. (2016)	Cocaine	32	L DLPFC	15 Hz	.8	Yes	No
Li et al. (2013b)	Meth.	10	L DLPFC	1 Hz	1 day	No	Within subject

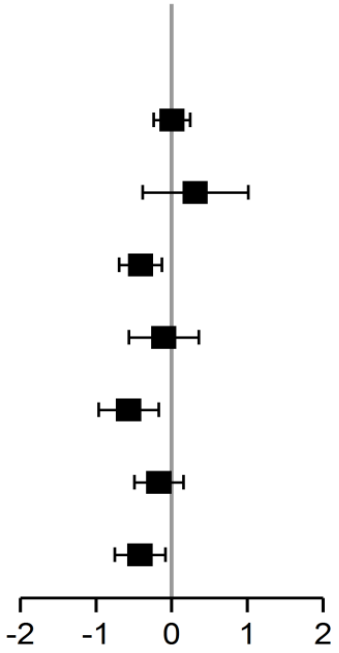
PFC, prefrontal cortex.

[a]Multiple sessions were given in a single day.

[b]Studies used H-coil TMS devices (Brainsway, Jerusalem, Israel). This deep TMS coil geometry has a very different field distribution than the typical figure of eight coils.

Repetitive Transcranial Magnetic Stimulation (rTMS) as a Promising Treatment for Craving in Stimulant Drugs and Behavioral Addiction: A Meta-Analysis. (Gay et al., 2022)

	SMD	95% CI	No
Alcohol	0.00	[-0.24; 0.24]	9-214
Cannabis	0.31	[-0.39; 1.01]	1-16
Nicotine	-0.41	[-0.70; -0.13]	8-140*
Cocaine	-0.11	[-0.57; 0.36]	2-36
Methamphetamine	-0.57	[-0.96; -0.18]	2-103
Eating disorder	-0.17	[-0.49; 0.15]	4-170*
Gambling disorder	-0.42	[-0.76; -0.08]	4-70*



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Repetitive transcranial magnetic stimulation in treatment-seeking subjects with cocaine use disorder: Randomized, double-blind, sham-controlled trial

(Martinotti et al., 2022)

80 subjects with CUD

15 Hz, left DLPFC

Accelerated daily 2 wk protocol with 12 weekly maintenance treatments

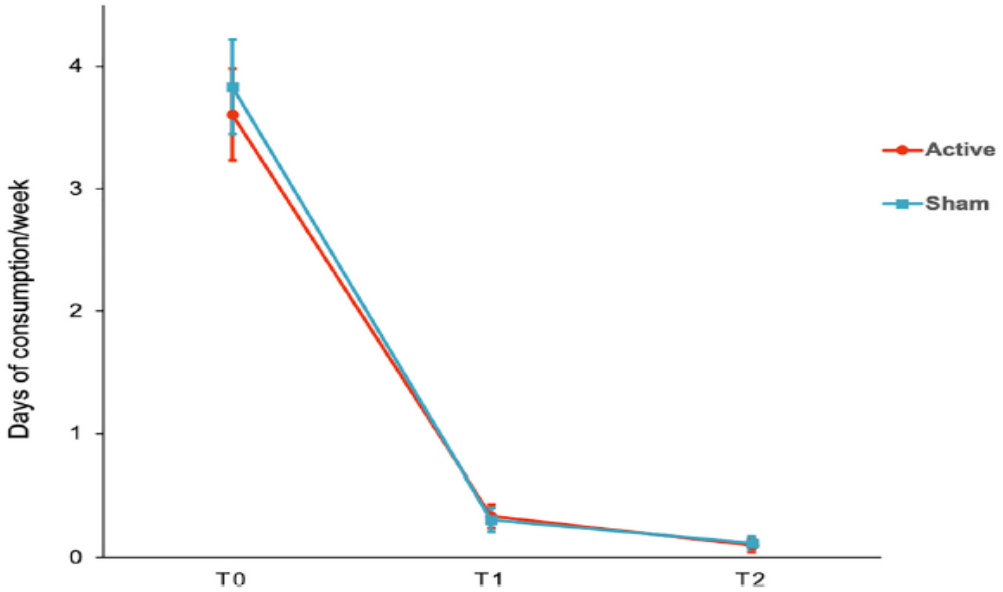

Fig. 3. Cocaine days of use (per week) during treatment in the two study groups (mean ± S.E.)

Adapted from Martinotti et al. (2022), licensed under Elsevier terms for reuse in academic and non-commercial contexts.

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South Carolina Clinical & Translational Research Institute

Randomized Controlled Trial of Medial Prefrontal Cortex Theta Burst Stimulation for CUD *(McCalley et al., 2024)*

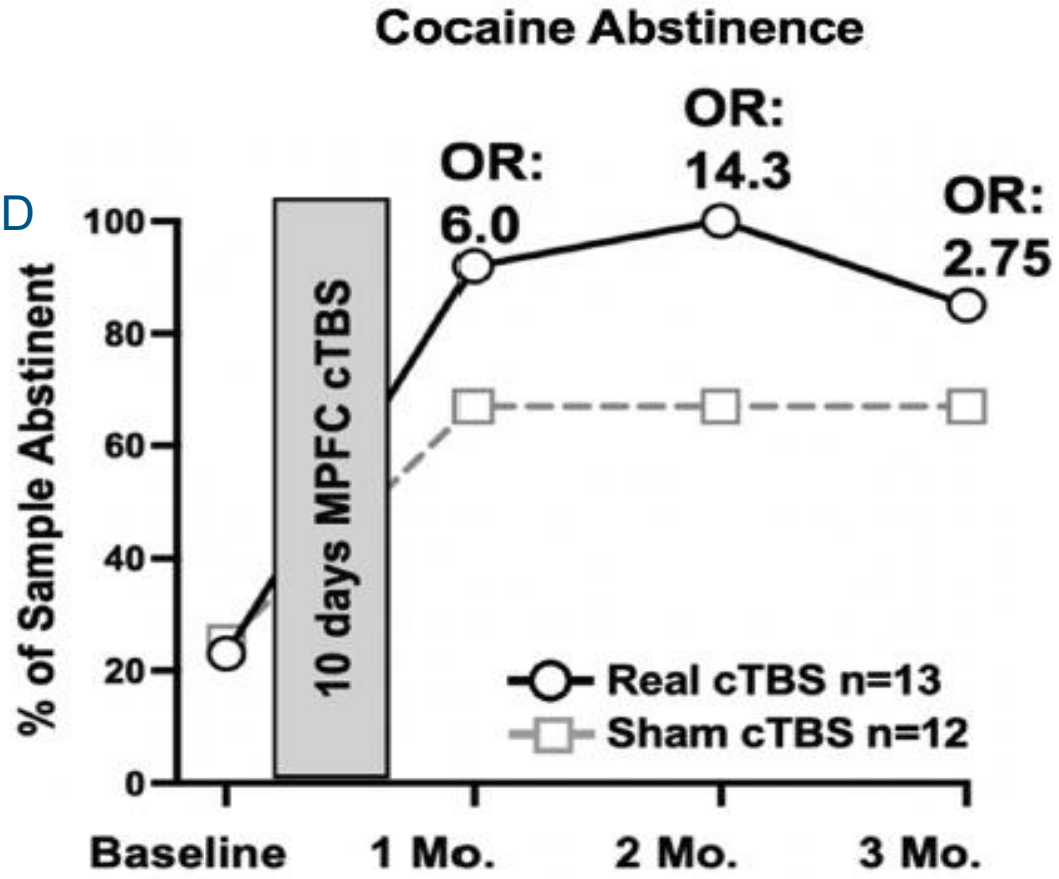
33 participants with CUD

10 sessions/3 weeks

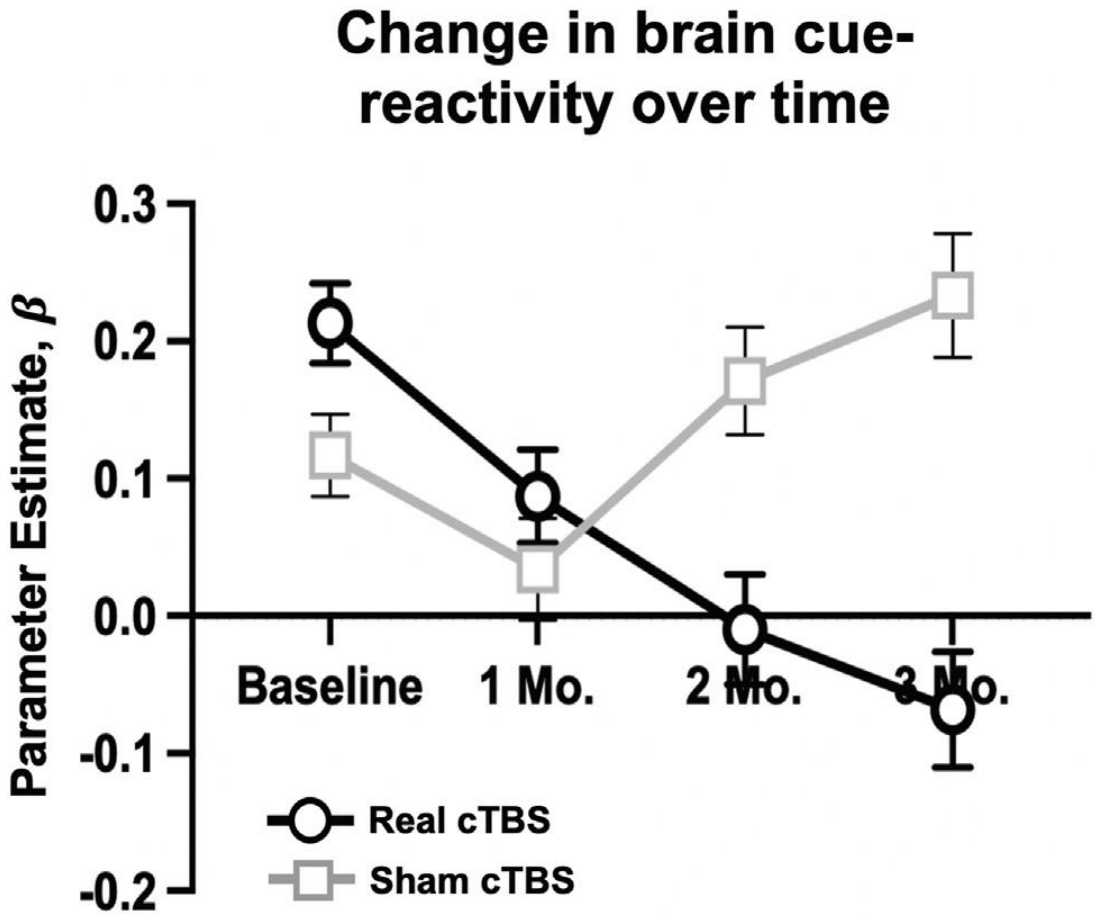
Brain reactivity to cues measured with fMRI

Increase abstinence in treatment group

Decreased craving in Treatment group



Biological Psychiatry: Cognitive Neuroscience and Neuroimaging June 2025; 10:616–625



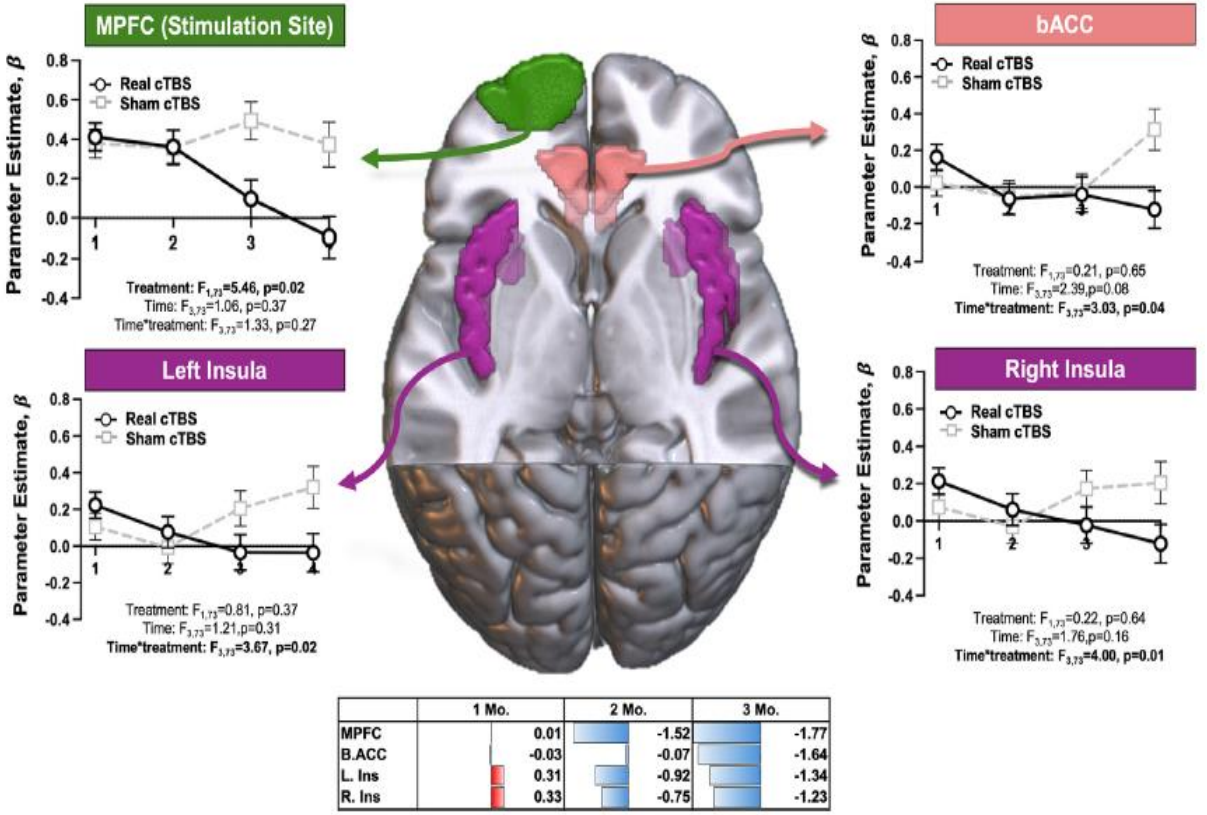
Biological Psychiatry: Cognitive Neuroscience and Neuroimaging June 2025; 10:616–625

Theta Burst Stimulation for CUD *(McCalley et al., 2024)*

Investigating mechanism decreased craving

Reduced activity in MPFC, insula and ACC correlated with craving decrease

Key nodes of salience network



Biological Psychiatry: Cognitive Neuroscience and Neuroimaging June 2025; 10:616–625

CTN-0108 rTMS for Stimulant Use Disorders

Lead Study Team

Study LIs

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Lead Team

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CCTN/NIDA

Geetha Subramaniam, MD

CTN-0108 rTMS for Stimulant Use Disorders

Study Sites

Medical University of South Carolina (MUSC), Charleston, SC

- Site PI: Karen Hartwell, MD

University of Texas Southwestern (UTSW), Dallas, TX

- Site PI: Manish Jha, MD

Wake Forest, Winston-Salem, NC

- Site PI: Colleen Hanlon, PhD/ Kristen O'Hearn, PhD

UT Health Science Center San Antonio (UTHSCSA), San Antonio, TX

- Site PI: Melissa Martinez, MD

CTN-0108 rTMS for Stimulant Use Disorders

Study Aims

Primary: Feasibility of up to 30 treatment sessions (rTMS v. Sham)

- **Outcome**: Percent of participants who obtained at least 20 treatment sessions
- **Hypothesis**: At least 75% of participants who enter CTN108 will receive 20 or more treatment sessions.

Secondary: Efficacy of up to 30 treatment sessions (rTMS v. Sham)

- **Outcome**: Percent negative of the last urine drug screen (UDS) per treatment week (7-day)
- **Hypothesis**: rTMS participants will have significantly higher percentage UDS negative results for primary substance of abuse (cocaine (CUD) or methamphetamine (MUD)) over the course of treatment compared to those in the sham group.

CTN-0108 rTMS for Stimulant Use Disorders

Exploratory Objectives

Additional Feasibility Measures

Impact of rTMS on:

- Self-reported substance use (TLFB)
- Craving
- Mood & Anxiety
- Sleep
- EEG
- Retention in Treatment
- Health, lifestyle, and functioning

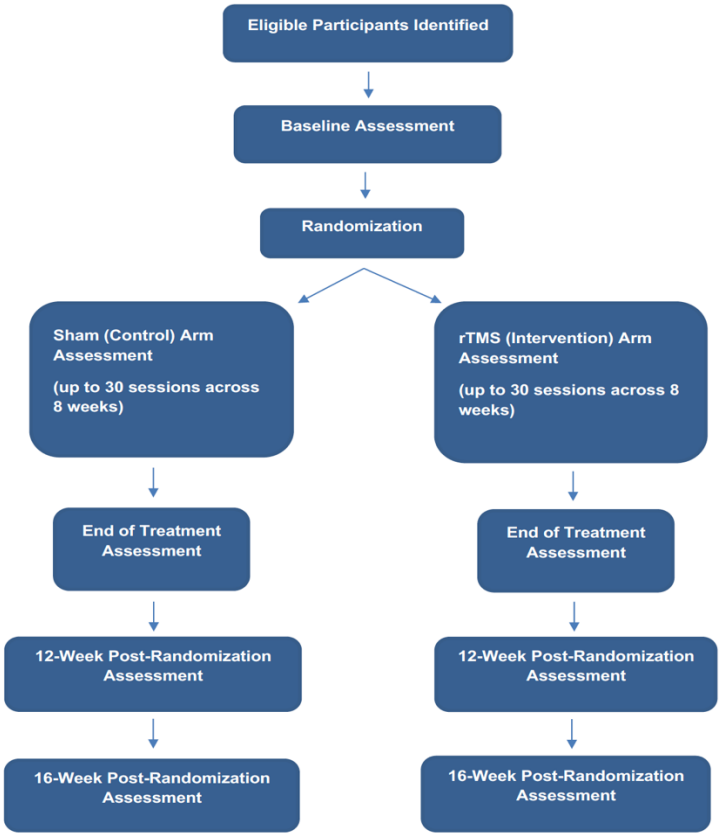
CTN-0108 rTMS for Stimulant Use Disorders

Overview of Protocol

Population: Methamphetamine and/or Cocaine Use Disorder : DSM-5 moderate to severe (N=160)
Groups will be stratified for depression and drug of choice, cocaine or methamphetamine
Dorsolateral Prefrontal Cortex (DLPFC)-focused high frequency repetitive Transcranial Magnetic Stimulation versus sham treatment
Double-blind with use of sham rTMS (coil simulates active, without delivering magnetic pulse)
Follow-up – 4 and 8 weeks after last TMS session
Pilot study: assess feasibility and assess for signal, inform decision-making for larger trial

CTN-0108 rTMS for Stimulant Use Disorders

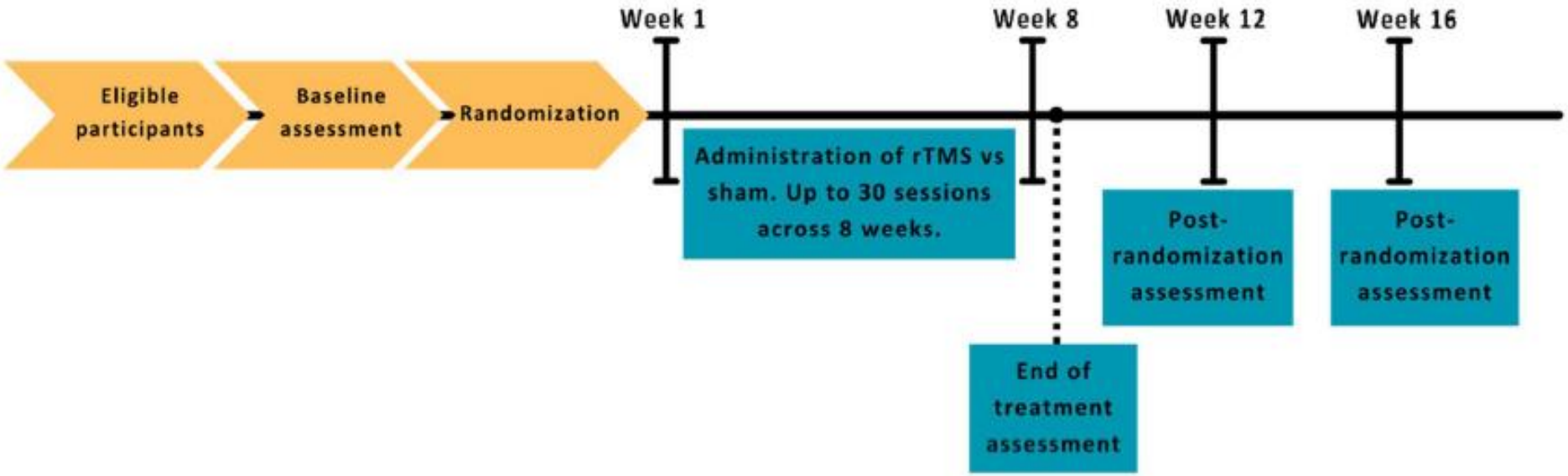
Overview of Study Design



- 160 Participants
  - 80 Cocaine Use Disorder (CUD)
  - 80 Methamphetamine Use Disorder (MUD)

4 Study Sites → 40 participants per site

Overview of Study Timeline
rTMS (Repetitive Transcranial Magnetic Stimulation)



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Study Population : Inclusion Criteria

Criterion	Rationale
1. Be aged 18-65, inclusive.	Defines study population.
2. Have a diagnosis of moderate or severe Cocaine or Methamphetamine Use Disorder (CUD/MUD) over the past 12 months (as determined by DSM-5 diagnostic criteria).	Recruiting participants with moderate or severe CUD or MUD will allow detection of rTMS versus sham effects, that may not be apparent with mild CUD or MUD.
3. Have used cocaine or methamphetamine on at least 10 of the last 30 days (based on TLFB).	Participants must have a current CUD or MUD.
4. Be interested in decreasing cocaine and/or methamphetamine use	Defines study population.
5. If female, willing to use appropriate birth control method during the treatment phase of the study (see list below).	Safety
6. Be able to understand the study procedures and provide written informed consent to participate in the study.	To comply with ethical standards, and to ensure adherence to study procedures, participants must be able to understand the study procedures, risks, and benefits.
7. If prescribed benzodiazepines or anticonvulsants, must be on a stable dose for at least 4 weeks prior to consent.	These medications can raise the seizure threshold, which could affect the motor threshold

CTN-0108 rTMS for Stimulant Use Disorders

Study Population: Exclusion Criteria

Criterion	Rationale
1. A DSM-5 diagnosis of moderate or severe SUD of any substance other than cocaine or methamphetamine based on DSM-5 Checklist.	The present study has been specifically designed to target, and assess effects of rTMS versus sham on, CUD or MUD. Defines study population.
2. History of a serious medical disorder that, in the opinion of the Medical Clinician, would make it unsafe to participate in the study or may prevent collection of study data.	Treatment for a serious medical disorder should take precedence over this experimental treatment for SUD. A serious medical disorder could interfere substantially with engagement in the treatment, negatively influencing feasibility and efficacy outcomes.
3. Is currently engaged in formal SUD treatment.	This pilot study is designed to examine the effects of rTMS (versus sham) in the context of a self-guided CBT program.
4. Documented history of unprovoked seizure (lifetime) or any seizure in the past 6 months.	Seizure is a risk associated with rTMS.
5. Documented history of brain lesion(s) and/or tumor(s).	The presence of a brain tumor or lesion might be a contraindication for rTMS (i.e., where seizure threshold is significantly lowered due to the lesion or if the lesion is on the rTMS-targeted cortical area).
6. Metal implants or non-removable metal objects above the waist.	Participant safety.
7. Currently pregnant.	While there is no available evidence to date suggesting that rTMS is harmful during pregnancy, the risks of using rTMS with pregnant women are unknown.
8. Lifetime history of prior clinical treatment with TMS	Prior TMS exposure will unblind active and sham groups.

CTN-0108 rTMS for Stimulant Use Disorders

rTMS Parameters

30 sessions over 8-week period – sessions offered daily, but allow for flexible delivery schedule; may have up to 2 sessions in 1 day

Coil placed over DLPFC using EEG coordinates, determine motor threshold every 10 sessions (more frequent if participant actively using or per MC assessment)

Exploring EEG as biomarker for treatment efficacy

Cue-reactivity session (using CUD/MUD use images) immediately before each TMS/sham session

CTN-0108 rTMS for Stimulant Use Disorders

rTMS Ramping Procedure

Key lesson learned to date from pilot, protocol amendment
Participants have up to 10 sessions to ramp to full dose
Participants not reaching full dose by end of tenth session will be continued in the study with their dose documented
Additional ramping (up to full dose) will be attempted every 5 sessions for participants not attaining full dose by session 10

CTN-0108 rTMS for Stimulant Use Disorders

Additional Components

Uses contingency management for active treatment and follow-up visits via remuneration for attending scheduled visits
Daily digital monitoring of craving, use, mood/stress, sleep via surveys
EEG at baseline and 4 weeks*
Sleep monitoring using actigraphy
Dynamicare platform for CBT education module delivery

Recruitment

Retention

Demographics

CTN-0108 rTMS for Stimulant Use Disorders

Prescreen, Screen, & Randomization

Site	Number of Pre-screens	Number of Screens	Number of Screen Fails	Percent that Screen Fail	Number in Screening	Number Eligible but Not Randomized	Number Randomized	Percent of Screens Randomized
SC Wake Forest	48	13	6	46%	0	0	7	54%
BSW University of Texas Southwestern	208	112	48	43%	0	5	59	53%
BSW UT Health San Antonio	449	99	77	78%	0	2	20	20%
SC MUSC Department of Psychiatry	425	120	73	61%	0	4	43	36%
Total	1130	344	204	59%	0	11	129	38%

Randomization by Primary SUD

Site	Number Randomized	Number Randomized with Primary Cocaine Use Disorder	Number Randomized with Primary Methamphetamine Use Disorder
SC Wake Forest	7	6 (86%)	1 (14%)
BSW University of Texas Southwestern	59	22 (37%)	37 (63%)
BSW UT Health San Antonio	20	3 (15%)	17 (85%)
SC MUSC Department of Psychiatry	43	22 (51%)	21 (49%)
Total	129	53 (41%)	76 (59%)

* Note: Wake Forest Site closed on June 27, 2023

CTN-0108 rTMS for Stimulant Use Disorders

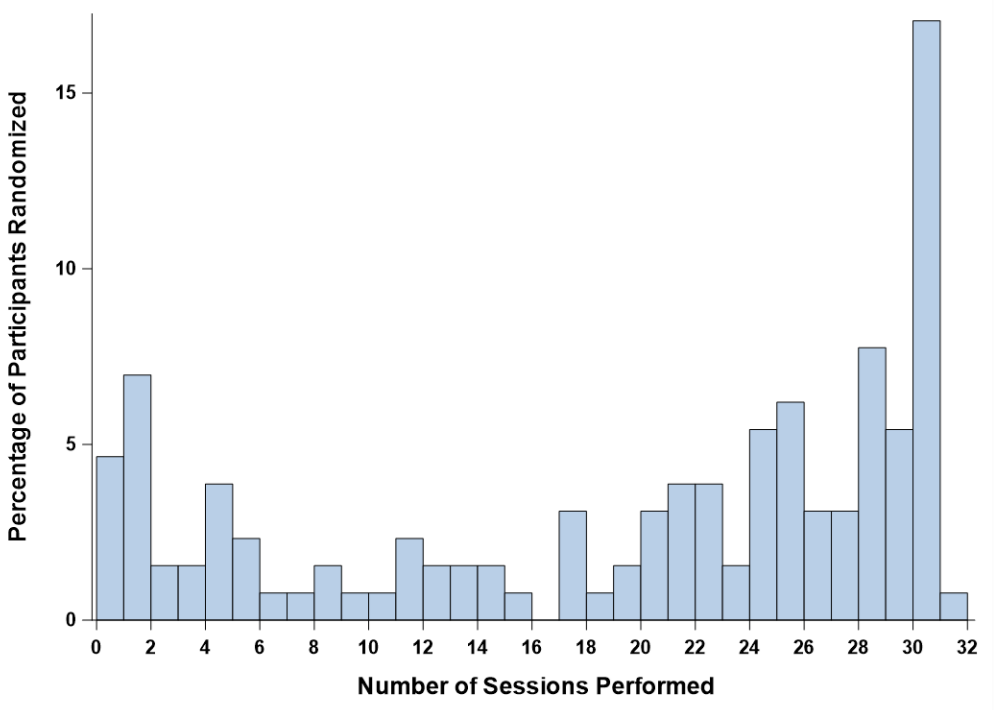
Retention: Active Treatment: 77%

Site	Number Randomized	Percentage who Attended Week 4 Visit [1]	Percentage who Attended EOT Visit [1]	Total
SC Wake Forest	7	86%	86%	86%
BSW University of Texas Southwestern	59	81%	81%	81%
BSW UT Health San Antonio	20	70%	75%	73%
SC MUSC Department of Psychiatry	43	76%	71%	73%
Total	129	78%	77%	77%

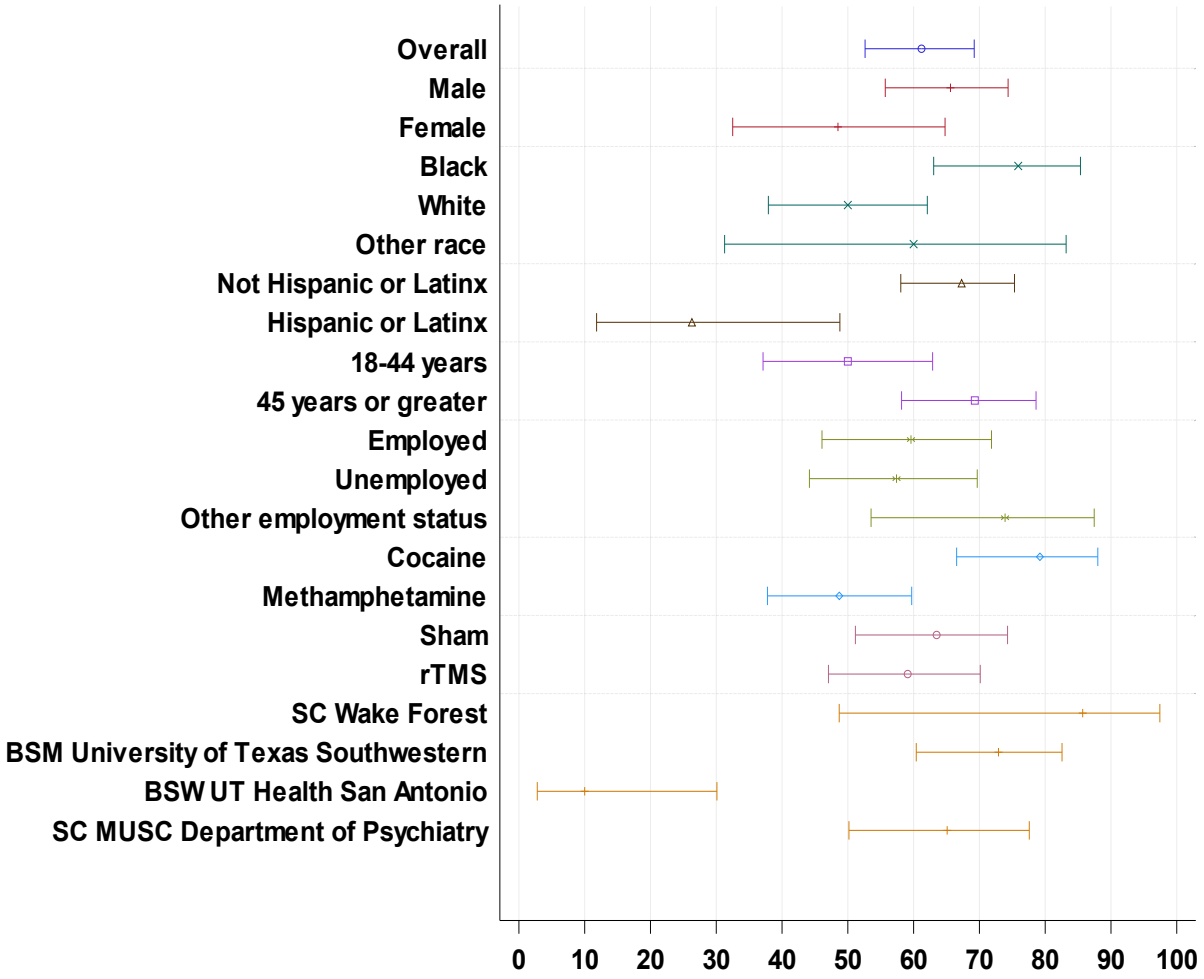
Retention: Follow-Up: 75%

Site	Number Randomized	Participants who Attended Week 12 Follow-up visit[1]	Participants who Attended Week 16 Follow-up visit[1]	Percentage of Follow-up Visits Attended[1]
SC Wake Forest	7	6/7 (86%)	6/7 (86%)	12/14 (86%)
BSW University of Texas Southwestern	59	39/52 (75%)	37/51 (73%)	76/103 (74%)
BSW UT Health San Antonio	20	15/20 (75%)	12/20 (60%)	27/40 (68%)
SC MUSC Department of Psychiatry	43	28/36 (78%)	27/33 (82%)	55/69 (80%)
Total	129	88/115 (77%)	82/111 (74%)	170/225 (75%)

NUMBER OF TMS SESSIONS

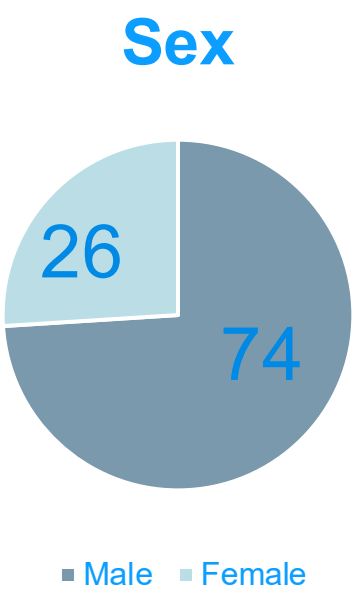


RETENTION RELATIONSHIP



CTN-0108 rTMS for Stimulant Use Disorders

Enrollment Demographics



Race	Study N	% of Enrolled Participants
American Indian or Alaska Native	1	1%
Black or African American	54	42%
Native Hawaiian or Pacific Islander	1	1%
White	62	48%
Other	3	2%
Multiple Race	5	4%
Missing or Unknown	3	2%

Polysubstance Use Per DSM-5 Checklist

Variable	Total	primary CUD	primary MUD	p-value
Group size	320	120 (37.5%)	200 (62.5%)	
Any SUD	105 (32.8%)	46 (38.3%)	59 (29.5%)	0.1
Alcohol SUD	43 (13.4%)	26 (21.7%)	17 (8.5%)	0.0008
Opioid SUD	18 (5.6%)	5 (4.2%)	13 (6.5%)	0.38
Marijuana SUD	33 (10.3%)	14 (11.7%)	19 (9.5%)	0.57
non-primary stimulant SUD	50 (15.6%)	24 (20%)	26 (13%)	0.11
other SUD	17 (5.3%)	4 (3.3%)	13 (6.5%)	0.31

SUD = moderate to severe use disorder per DSM-5

Polysubstance Use Per TLFB

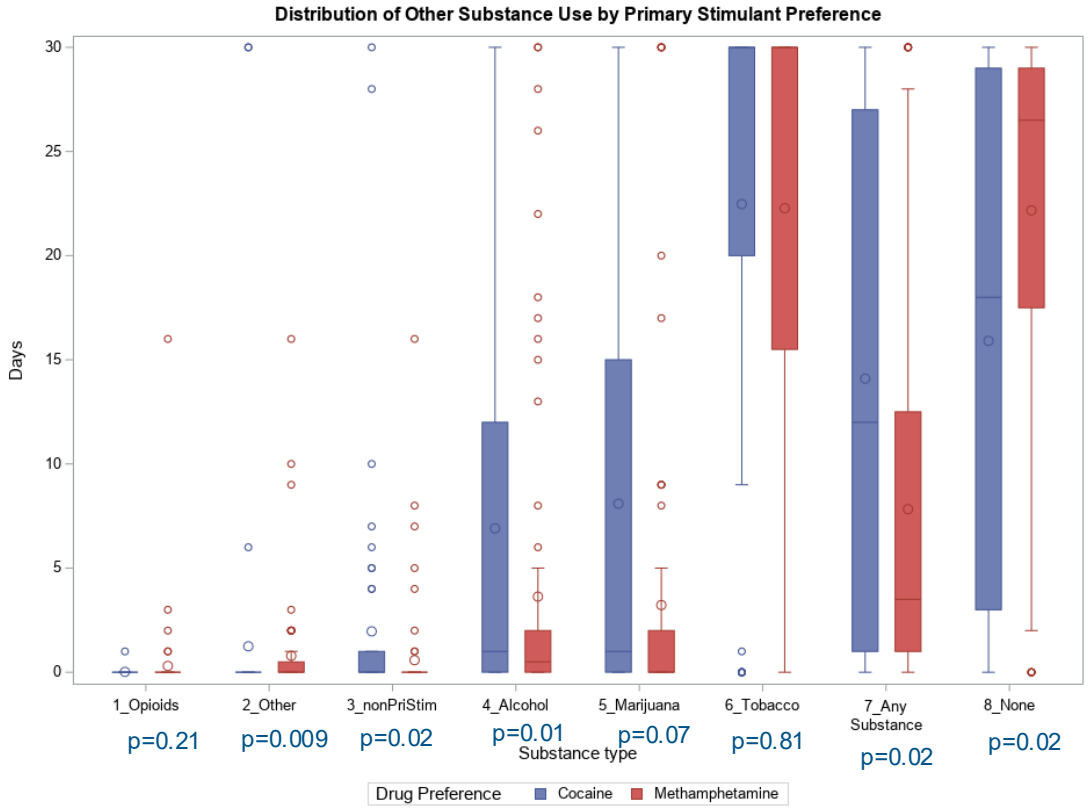
	Substance use per TLFB (N=129)		
	Primary CUD (N=53)	Primary MUD (N=76)	p-value
Any	45 (84.9%)	61 (80.3%)	0.64
Tobacco	44 (83.0%)	58 (76.3%)	0.39
Alcohol	36 (67.9%)	38 (50.0%)	0.048
Opioid	1 (1.9%)	5 (6.6%)	0.40
Marijuana	27 (50.9%)	35 (46.1%)	0.60
Non-Primary Stimulant	14 (26.4%)	8 (10.5%)	0.03
Other	3 (5.7%)	19 (25%)	0.004
Primary Stimulant	53 (100%)	76 (100%)	NA
None	8 (15.1%)	15 (19.7%)	0.64

- Any = any substance other than the primary stimulant, excludes tobacco
- Other = combined reporting from sedatives, benzodiazepines, hallucinogens, inhalants, club drugs

First substance used

Table of drugPref by first reported substance use at earliest age of use											
		subs									Total
		none	ALC	BZO	COC	HAL	INH	PNK	STM	THC	
drugPref(Stimulant choice)											
Cocaine	Frequency	1	16	0	0	2	1	0	0	33	53
	Percent	0.78	12.4	0	0	1.55	0.78	0	0	25.58	41.09
	Row Pct	1.89	30.19	0	0	3.77	1.89	0	0	62.26	
	Col Pct	100	29.63	0	0	33.33	50	0	0	53.23	
Methamphetamine	Frequency	0	38	1	1	4	1	1	1	29	76
	Percent	0	29.46	0.78	0.78	3.1	0.78	0.78	0.78	22.48	58.91
	Row Pct	0	50	1.32	1.32	5.26	1.32	1.32	1.32	38.16	
	Col Pct	0	70.37	100	100	66.67	50	100	100	46.77	
Total	Frequency	1	54	1	1	6	2	1	1	62	129
	Percent	0.78	41.86	0.78	0.78	4.65	1.55	0.78	0.78	48.06	100

Median days of use per TLFB



Discussion Points

CUD group (N=320) had more moderate to severe comorbid alcohol use disorder

Even in the randomized cohort, where people with moderate to severe comorbid substance use (aside from tobacco) were excluded, polysubstance use was still very prevalent

Future direction: importance of investigating the safety of treatment interventions in populations with polysubstance use

CONCLUSIONS/FUTURE DIRECTIONS

Neuromodulation shows promise in the treatment of stimulant use disorders

Many unanswered questions:

- ? Accelerated treatment
- ? Refining frequencies and patterns – theta burst
- ? Durability, maintenance

CTN-0108 will provide valuable information

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