Transcranial Magnetic Stimulation in the Treatment of Stimulant Use Disorders

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Disclosure Information (Required)

TMS in Stimulant Use Disorders

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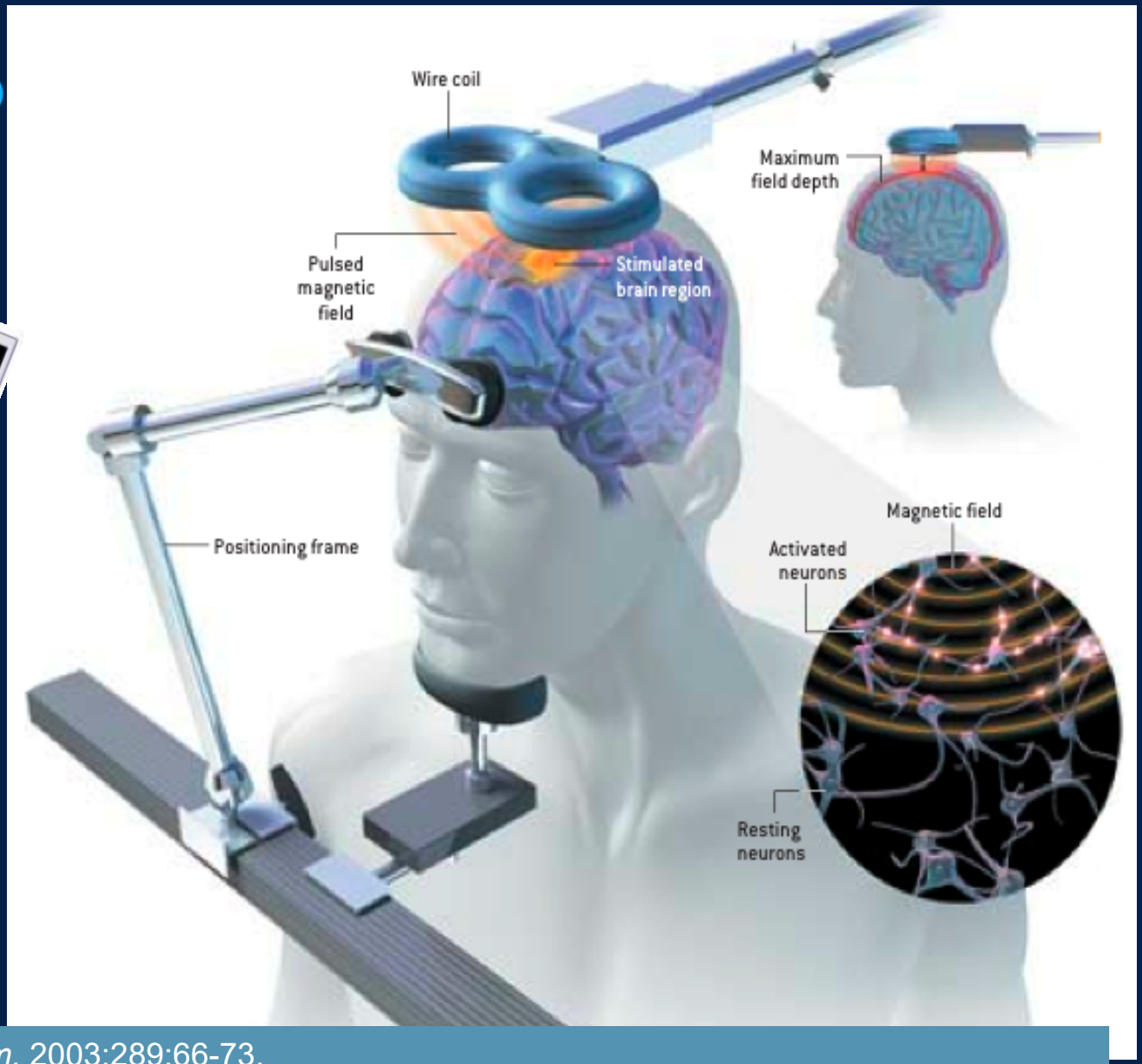
- No Disclosures

Learning Objectives (Suggested)

- To learn about basic principles underlying transcranial magnetic stimulation (TMS)
- To learn about data to date supporting the use of TMS in the treatment of stimulant use disorders
- To discuss “next steps” in exploration of the use of TMS in the treatment of stimulant use disorders

What Is TMS?



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

TRANSCRANIAL MAGNETIC STIMULATION

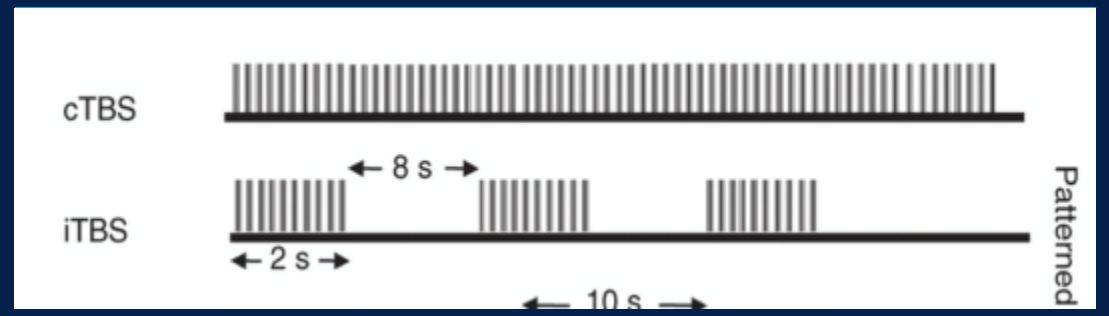
Non-invasive form of brain stimulation - changing magnetic field is used to cause electric current in specific brain regions through electromagnetic induction

Behavioral and Brain effects are frequency dependent

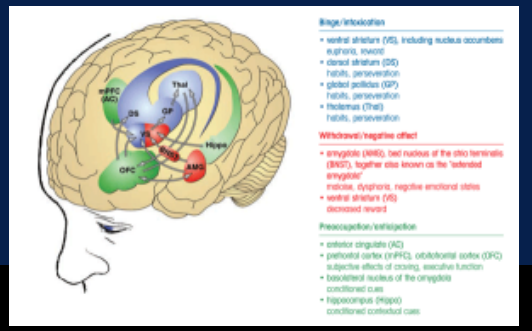
Frequency dependent modulation of cortical targets		
High Frequency (10Hz) Intermittent Theta Burst	higher cortical excitability	Amplified neural response
Low Frequency (1Hz) Continuous Theta Burst	lower cortical excitability	Attenuated neural response

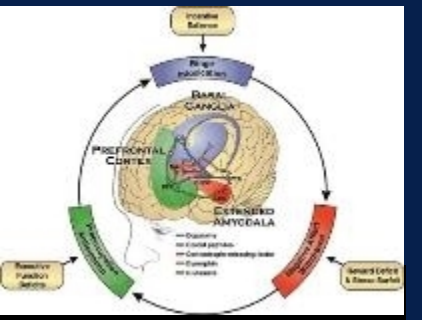
Standard, fixed rate TMS

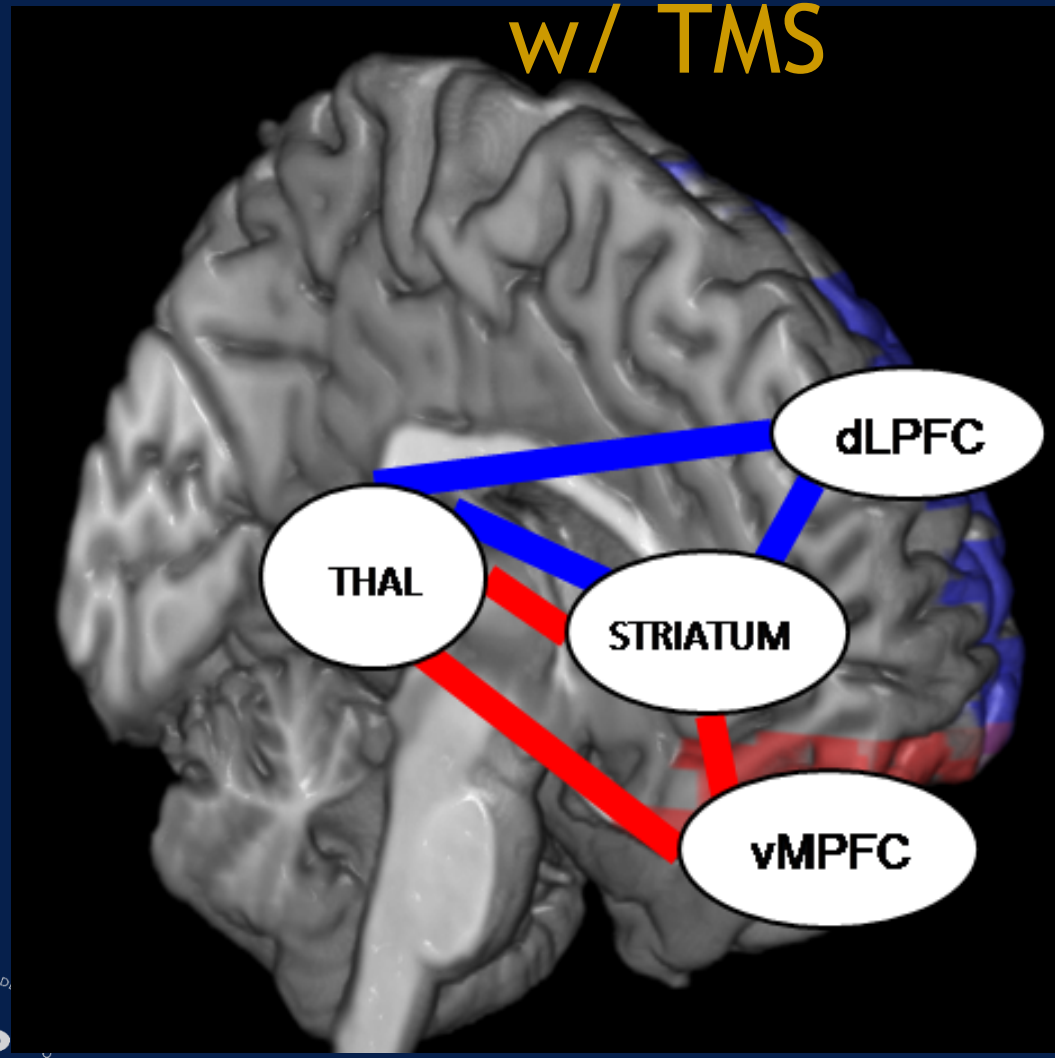
Accelerated, theta burst TMS



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

Stimulation in Addiction

(Sailing and Martinez, Neuropharm; 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 6	R DLPFC L DLPFC	10 Hz, 90% MT 10 Hz, 90% MT	Craving Craving	↓ No effect	Camprodon *et al*, 2007
	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

Modulating Neural Circuits with Transcranial Magnetic Stimulation: Stimulant Use Disorder (Hanlon et al., Pharmacol Review, 2018)

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.

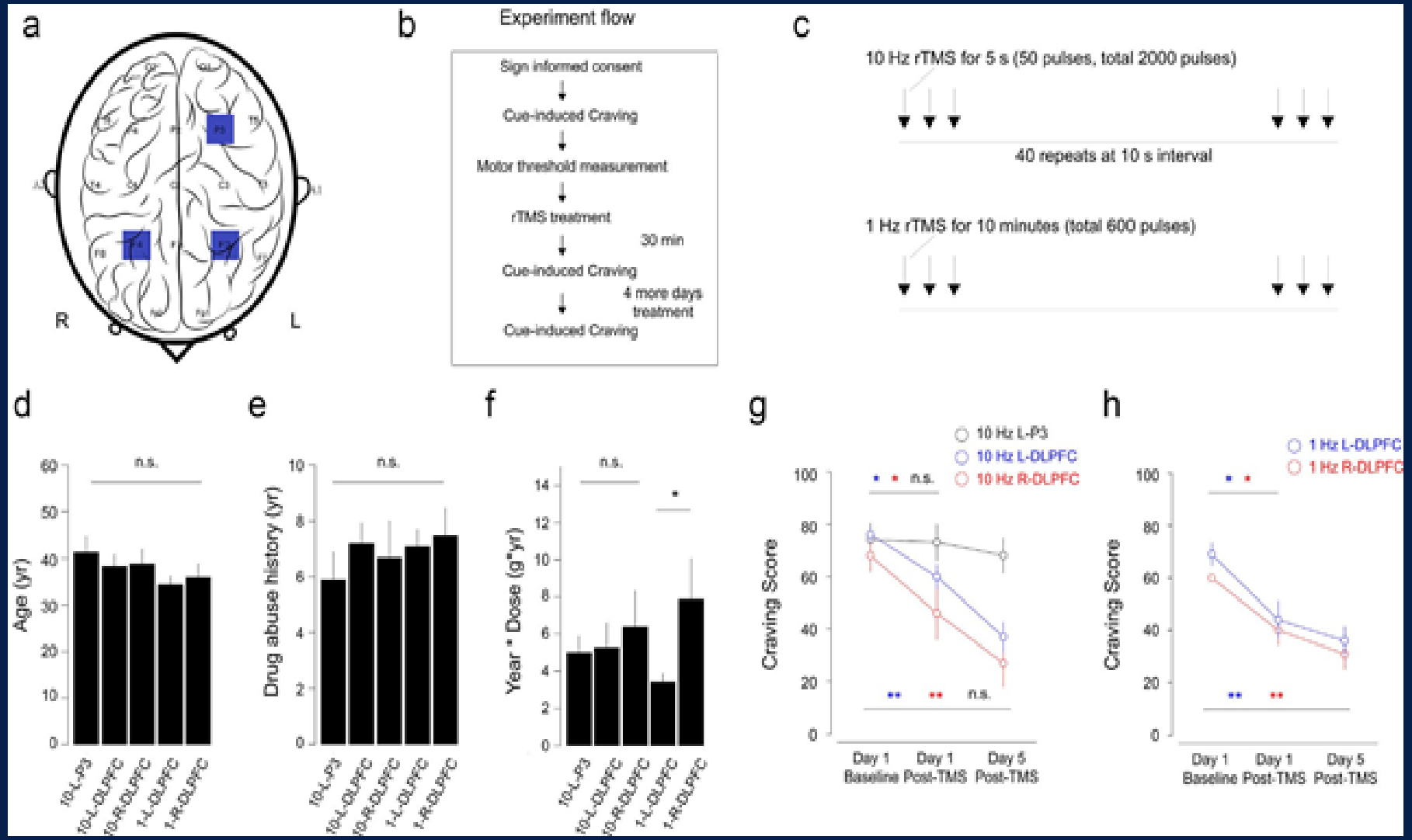
Either Left or Right, Both High and Low Frequency rTMS of Dorsolateral Prefrontal Cortex Decreases Cue Induced Craving for Methamphetamine

(Lui et al., 2017)

50 males with MUD

Daily treatment for 5 days

Craving measured immediately before and 30 min after treatment



Targeting Withdrawal Symptoms in MUD: Randomized Trial

Liang et al., 2018

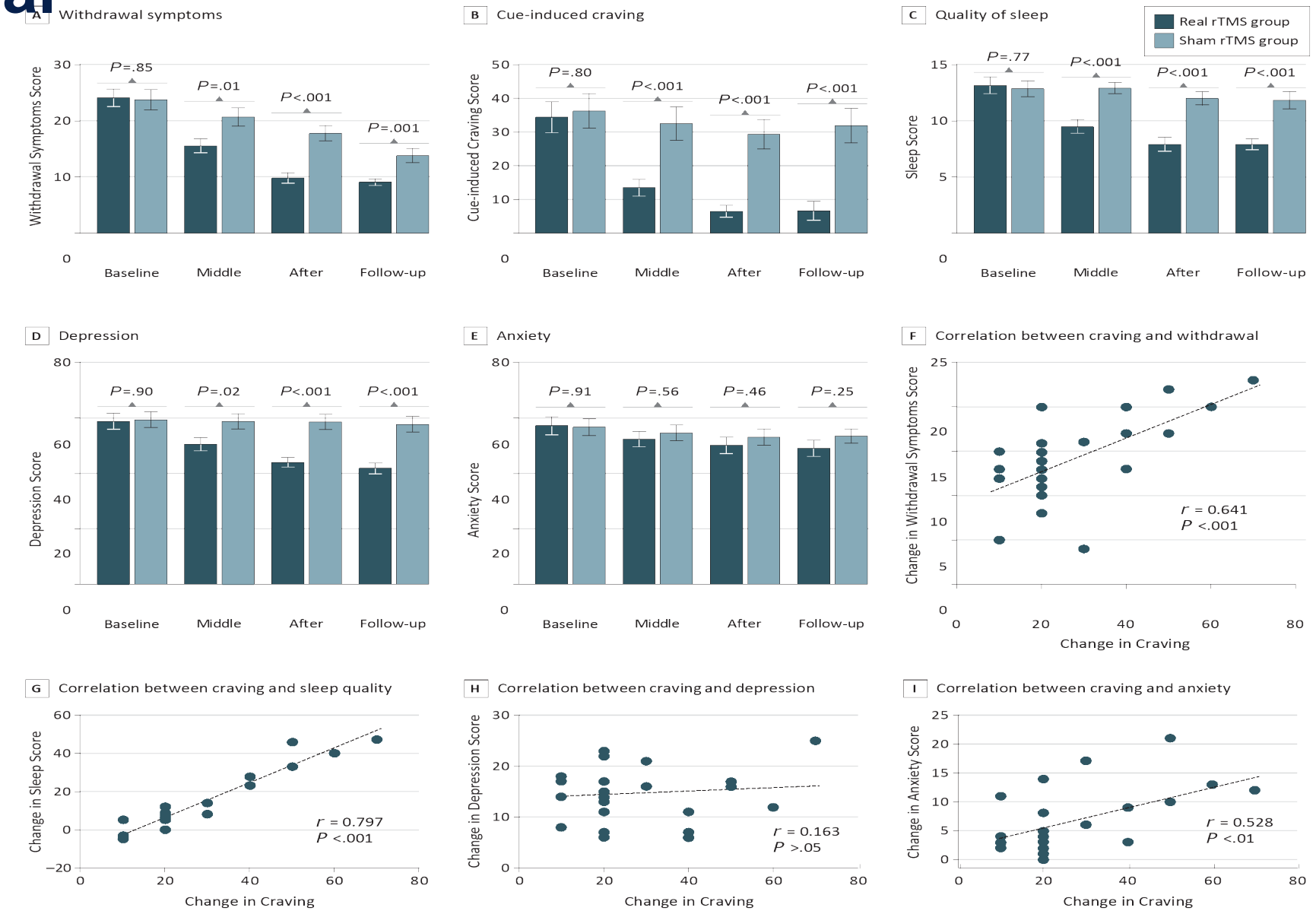
50 men with MUD

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 ($F_{3,1}$ 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

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 treatment, 60 days post

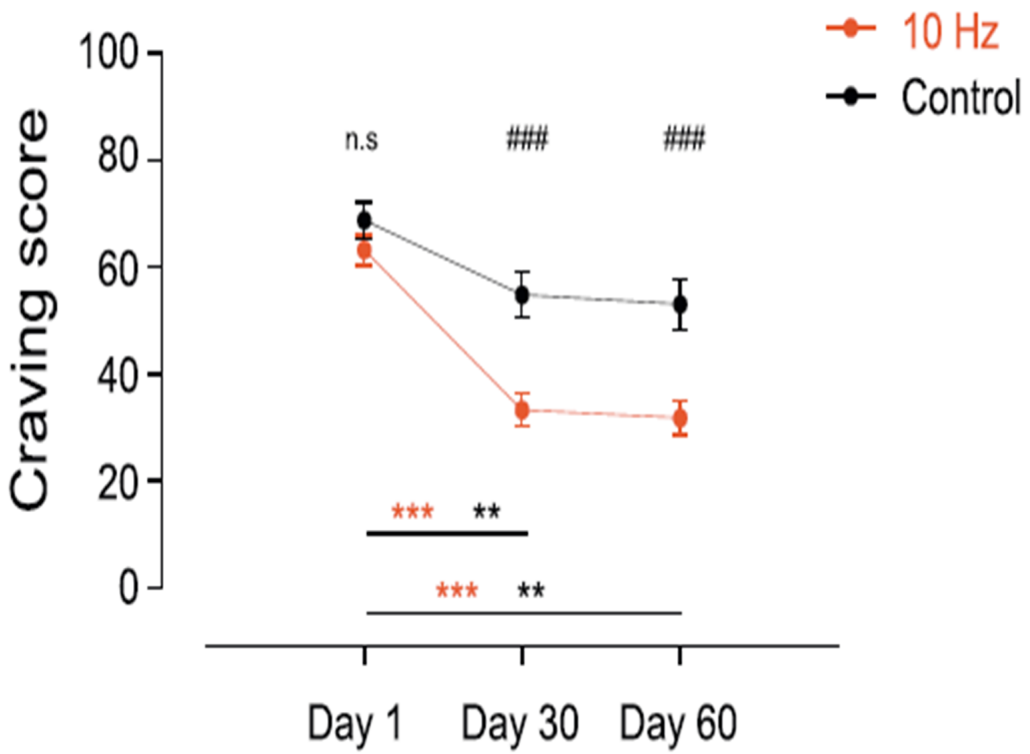


Fig. 3. The effect of rTMS in 10 Hz and control group. Inter group difference (# for $p < .05$, ## for $p < .01$ and ### for $p < .001$), and intra group difference (* for $p < .05$, ** for $p < .01$ and *** for $p < .001$) were showed. There were significant differences between 10 Hz group and control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

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

All good science leads to more questions: Currently approximately 220 TMS in SUD articles since 2000

- Dose: 20 or more sessions in depression
- Frequency: 10 Hz most commonly used
- Target: DLPFC
- Durability
- Impact on use (not only craving)
- ?Maintenance treatments
- Adjunctive therapies

CTN 108: rTMS in Stimulant Use Disorder
K Brady/M Trivedi Co-PI

- 4 Site Trial
- N=120, methamphetamine or cocaine use disorder
- Daily digital monitoring of craving, use, mood/stress, sleep
- CBT digital modules available
- Primary Outcome: Feasibility of 30 sessions of rTMS (v. Sham)
- Secondary: Efficacy of up to 30 sessions of rTMS (v. Sham)
  - **Outcome**: Percent negative of the last UDS per treatment week (7-day)

Clinical Trial of rTMS in Stimulant Use Disorder: TMS Parameters

- 30 sessions over 6-8 week period
- sessions offered daily, but allow for flexible delivery schedule; may have 2 sessions in 1 day, must have at least 4 sessions per week
- Coil placed over DLPFC using EEG coordinates, determine motor threshold weekly (more frequent if participant actively using)
- Exploring EEG as biomarker for treatment efficacy
- Cue-reactivity session immediately before each TMS/sham session

ONWARD AND UPWARD

- Very promising therapy
- MUCH progress made in last 20 years
- Need:
  - Sham controlled, adequate sample size
  - Dose–comparison studies
  - Durability studies
  - Ancillary/concommitant treatment

References

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