Transcranial Magnetic Stimulation in the Treatment of Methamphetamine Use Disorder

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- DISCLOSURES:
- Indivior Pharmaceuticals, Paid Consultant
- Embera Pharmaceuticals, Paid Consultant
- Alkermes Pharmaceuticals, Paid Consultant
- Sage Pharmaceuticals, Paid Consultant

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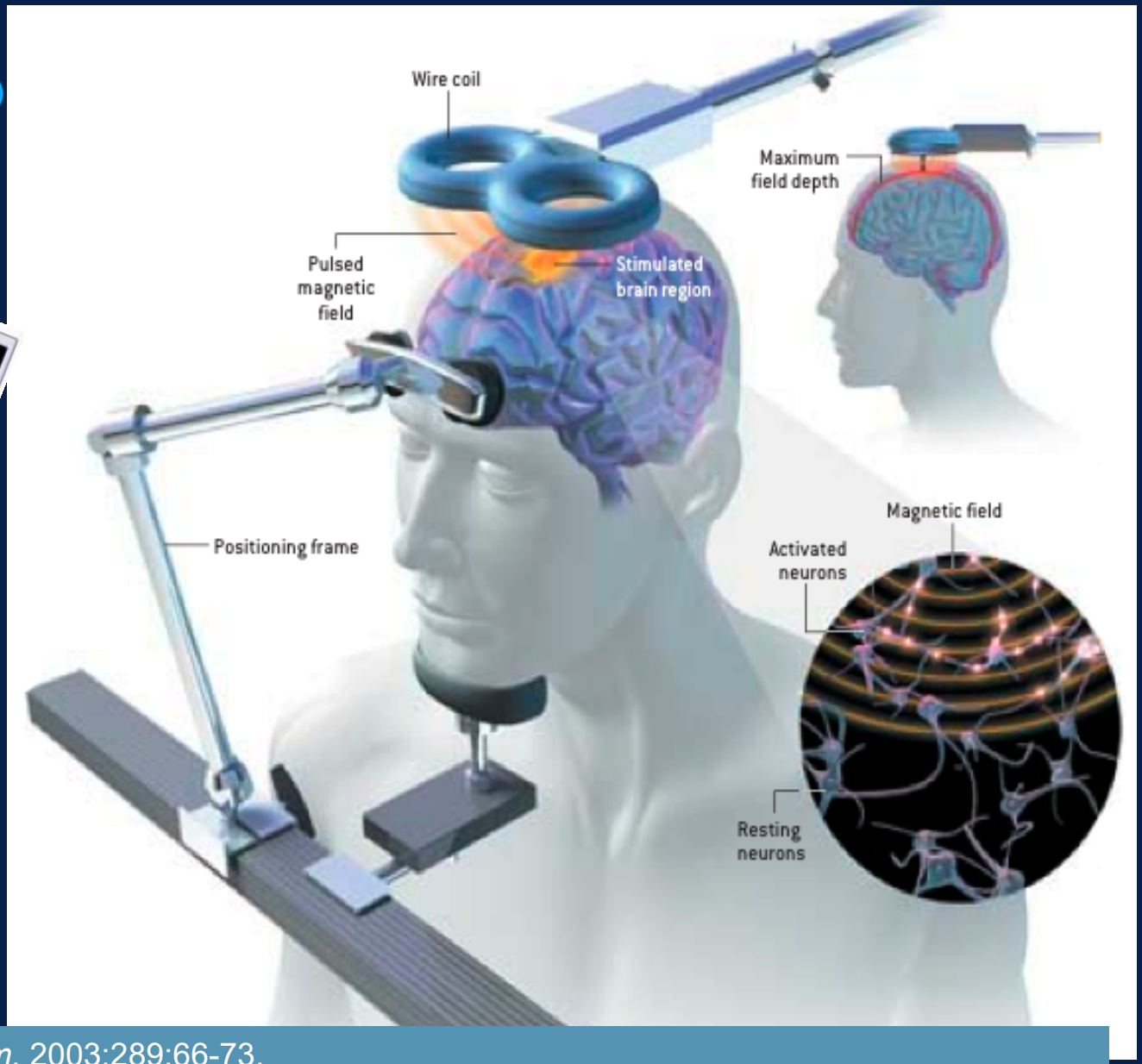
What Is TMS?



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

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

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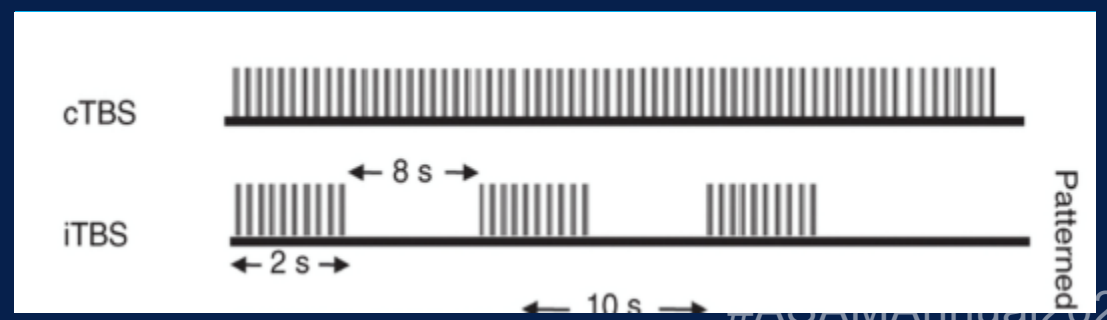
Behavioral and Brain effects are frequency dependent

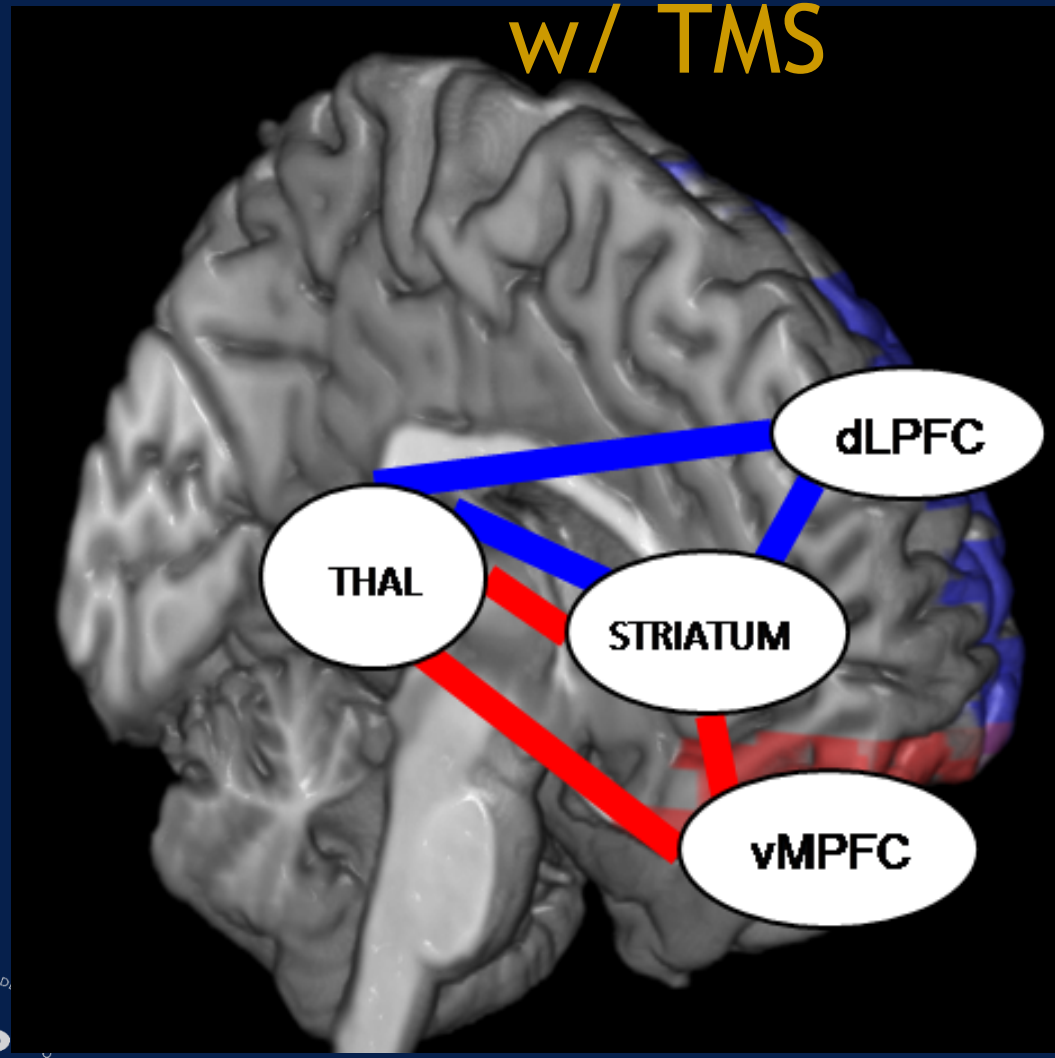
Frequency dependent modulation of cortical targets		
High Frequency (10Hz) Intermittent Theta Burst	higher cortical excitability	Amplified neural response
Low Frequency (1Hz) Continuous Theta Burst	lower cortical excitability	Attenuated neural response

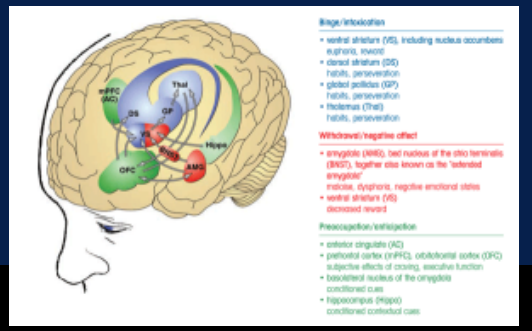
Standard, fixed rate TMS

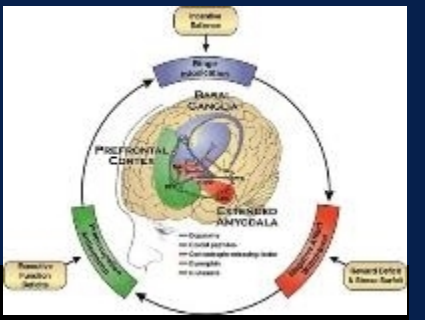
Accelerated, theta burst TMS



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

Hanlon, SMBT 2012, Oral Poster

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 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

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

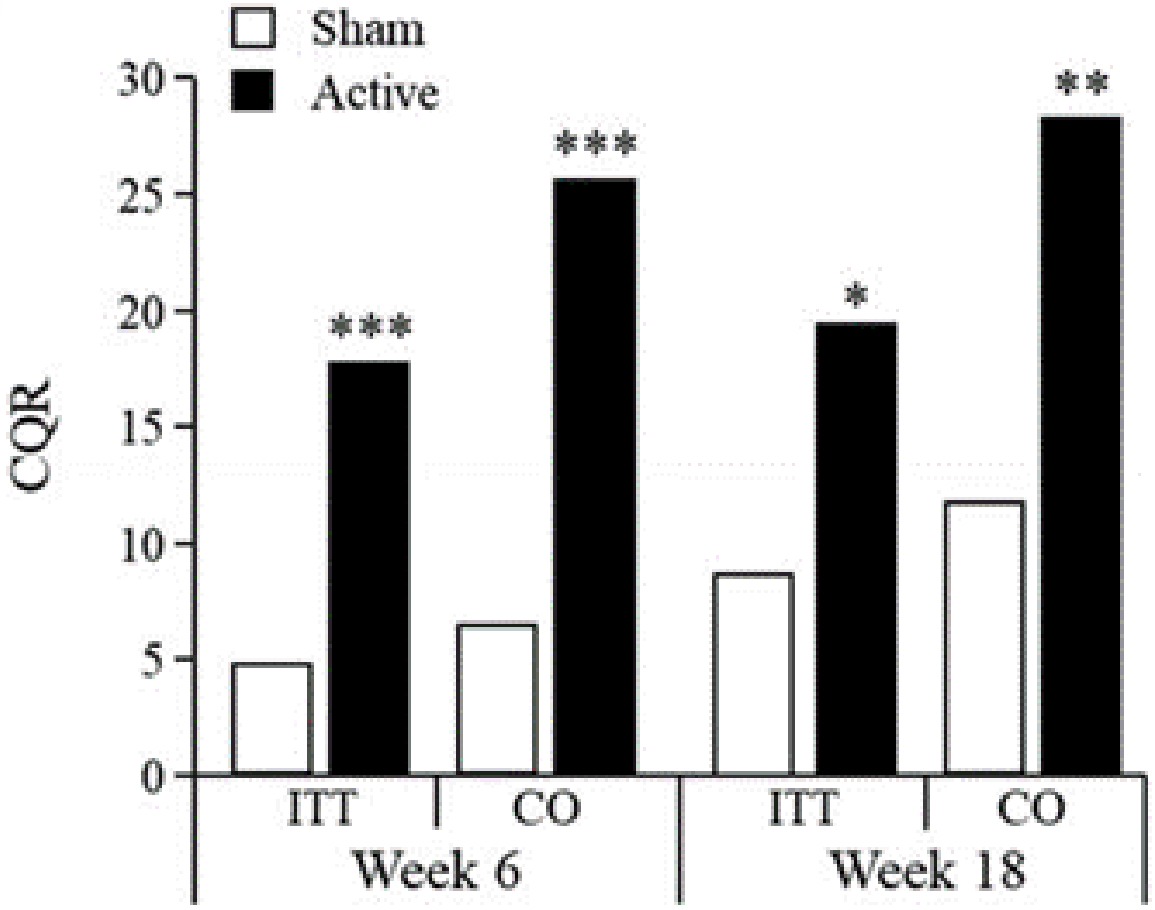
Randomized, double-blind multi-center trial

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



Modulating Neural Circuits with Transcranial Magnetic Stimulation: Stimulant Use

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.

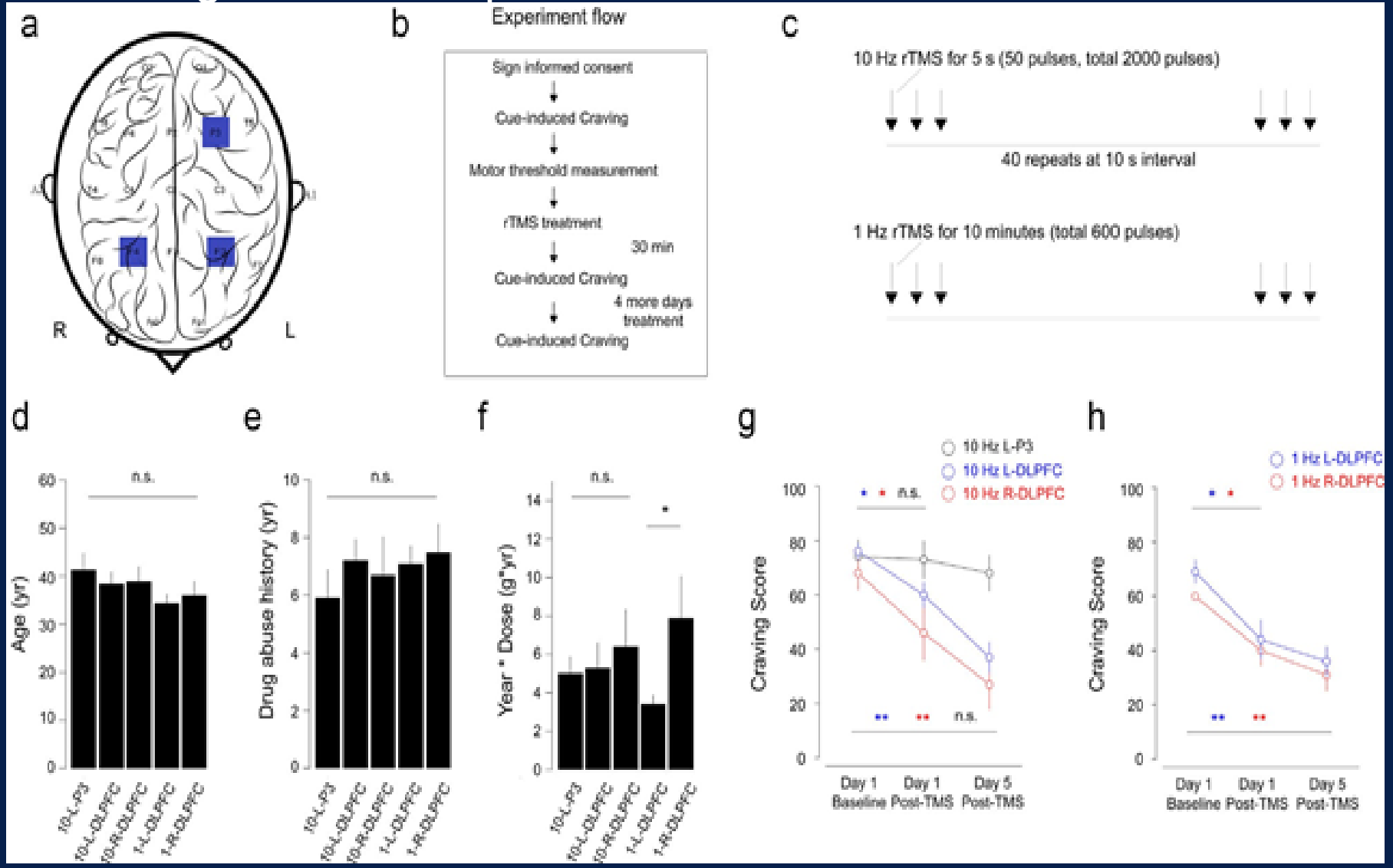
[a]Multiple sessions were given in a single day.

[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 Clinical Trial

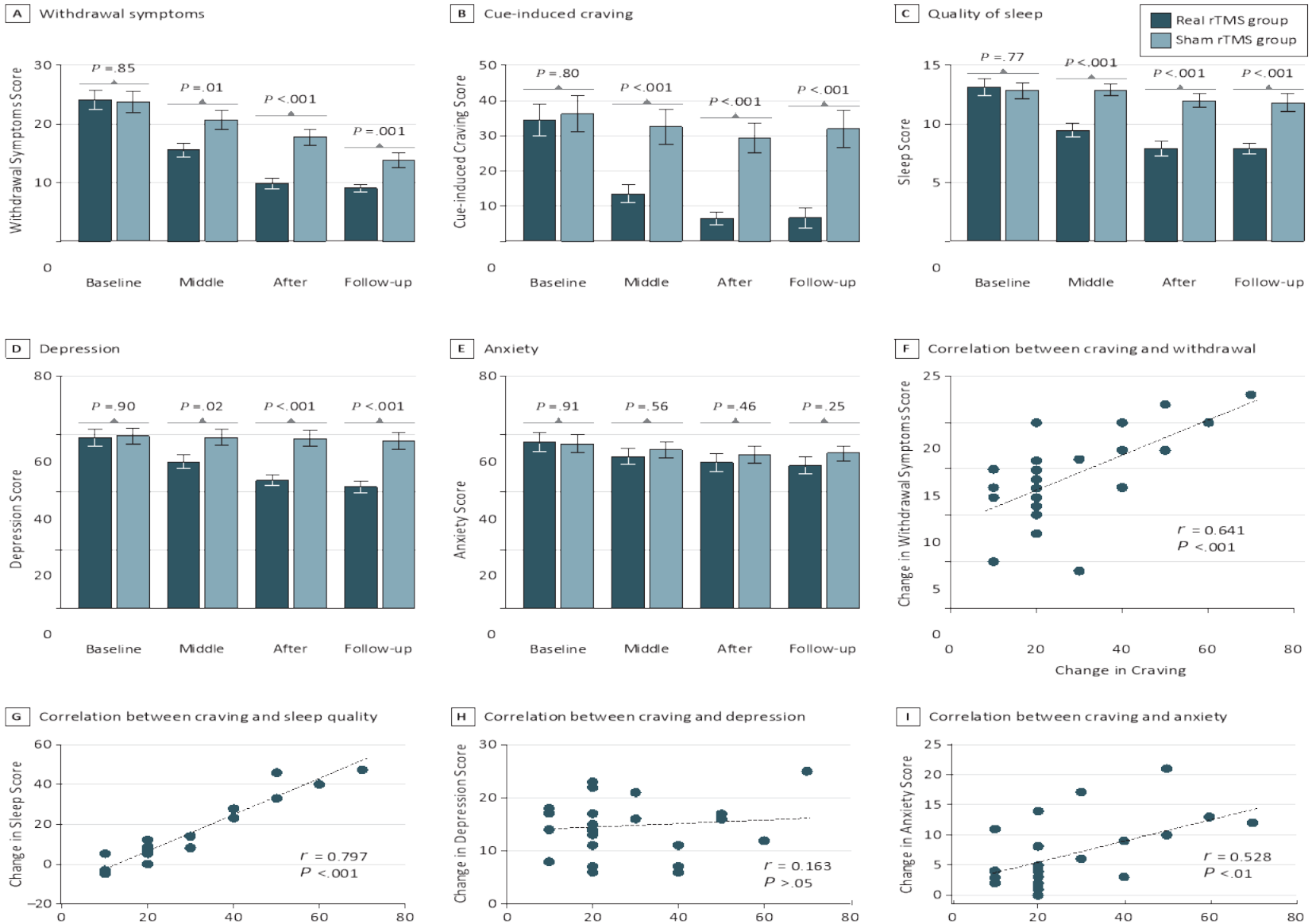
Liang et al., 2018

50 men with MUD

Sham-controlled

10 Hz trt L DLPFC

10 treatments over 12 days



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

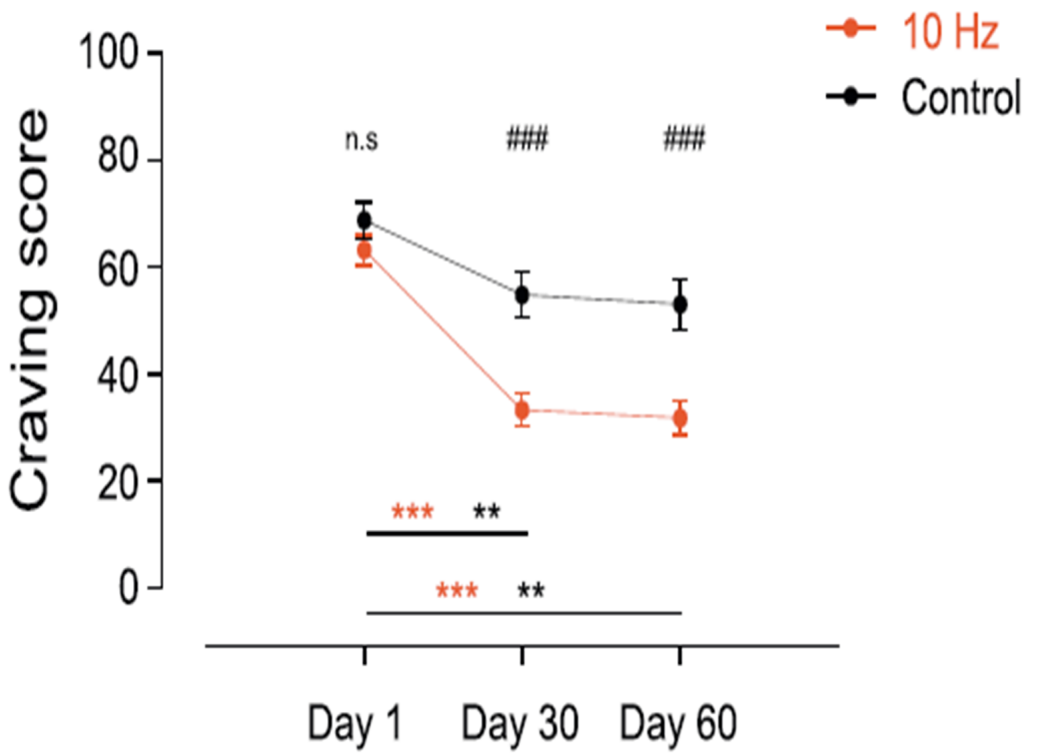


Fig. 3. The effect of rTMS in 10 Hz and control group. Inter group difference (# for $p < .05$, ## for $p < .01$ and ### for $p < .001$), and intra group difference (* for $p < .05$, ** for $p < .01$ and *** for $p < .001$) were showed. There were significant differences between 10 Hz group and control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

All good science leads to more questions: Currently approximately 200 TMS in SUD articles since 2000

- Dose: 20 or more sessions in depression
- Frequency: 10 Hz most commonly used
- Target: DLPFC
- Durability
- ?Maintenance treatments
- Adjunctive therapies

CTN 108: rTMS in Stimulant Use Disorder

K Brady/M Trivedi Co-PI

- N=160, methamphetamine or cocaine use disorder
- DLPFC-focused 10 Hz rTMS vs sham
- 30 sessions over 8-week period – flexible delivery schedule
- Cue-reactivity before each session/exploring EEG as biomarker
- 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)

References (Required)

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5. Liu T, Li Y, Shen Y et al. Gender does not matter: Add-on repetitive transcranial magnetic stimulation treatment for female methamphetamine dependents.2019, Progress in Neuropsychopharm, 92, 70-75.