Transcranial Magnetic Stimulation (TMS)

Diana Martinez, MD
New York State Psychiatric Institute
Columbia University Irving Medical Center
dm437@cumc.coumbia.edu

Origins of TMS

The development of TMS began with ECT (electroconvulsive therapy).

ECT came into use almost 100 years ago, when it was found that brain stimulation and seizure improved symptoms of serious mental illness.

ECT remains in use for patients with severe depression (also bipolar disorder, catatonia, psychosis) who do not improve with other treatments.

However, it has side effects and requires anesthesia:

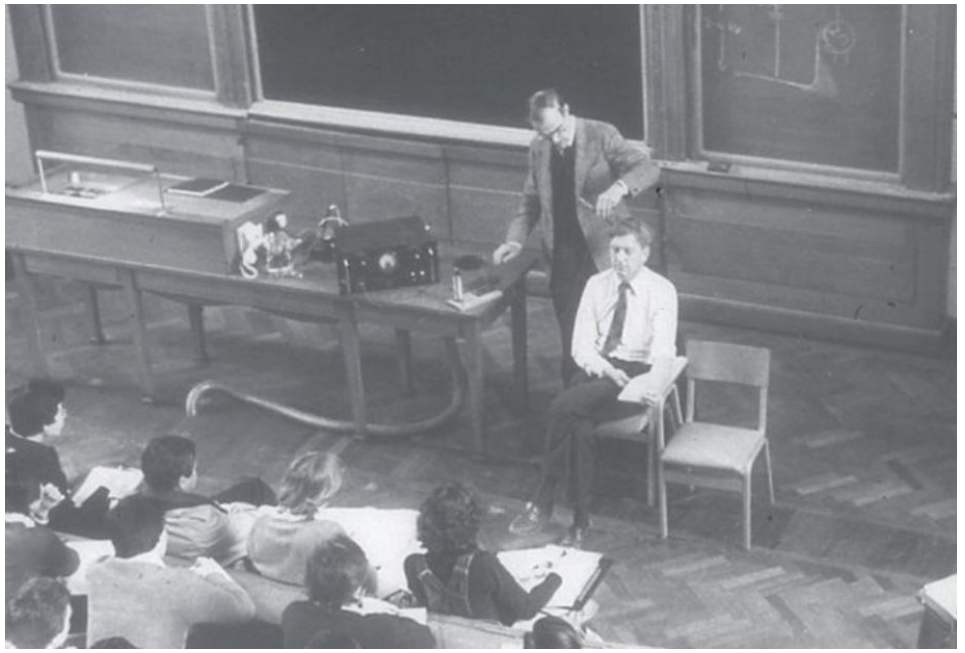
- Memory impairment - that gets better over 2-3 weeks
- Requires anesthesia because of the seizure it causes

TMS began by researchers trying to find out if brain stimulation without a seizure could improve psychiatric symptoms

Origins of TMS

Investigators (Merton and Morton) experimented with delivery of electrical stimulation, without seizure, to brain – without anesthesia (1980).

- They delivered stimulation to the brain - but found that only a fraction of the stimulation gets through the skull, and most goes to the scalp (muscles and skin) which was painful.



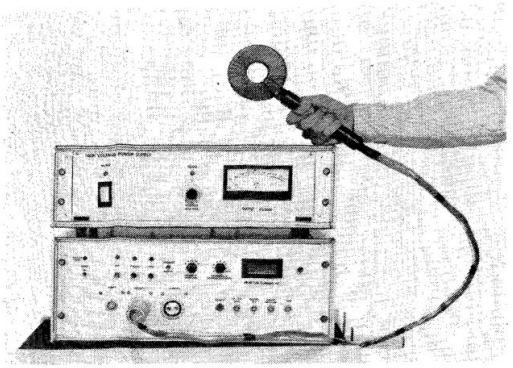
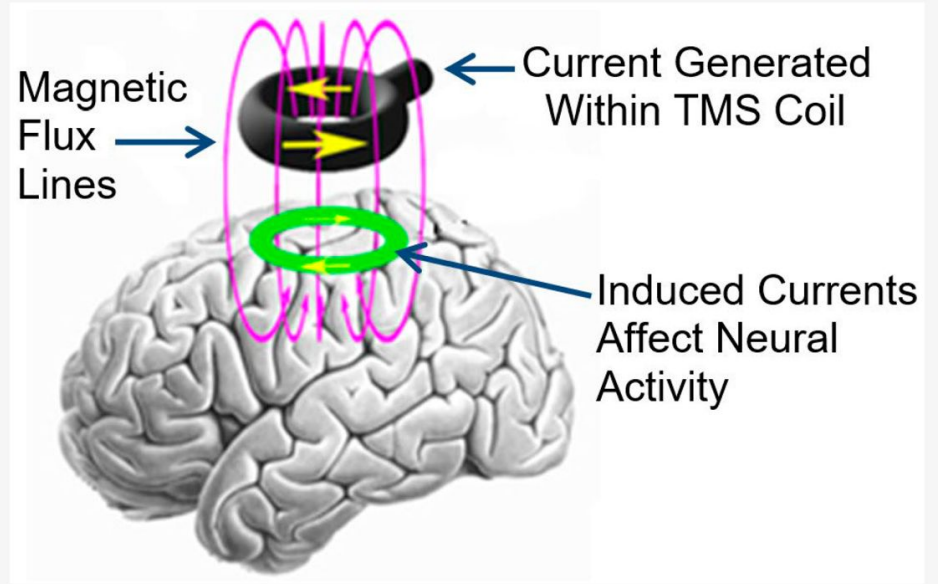
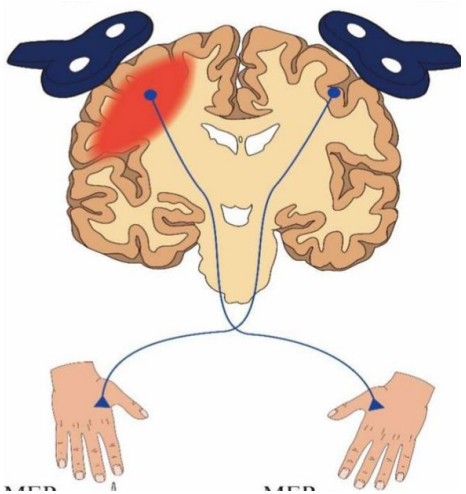


Fig 1—Magnetic stimulator and coil.

Anthony Barker and colleagues developed the first TMS device for research applications in 1985. It used a magnetic field to cross through the skull instead of an electrical field.

TMS: How It Works





- A large wire coil positioned near to the scalp, an electrical current passes through in pulses.
- The electrical field generates magnetic field, travels through skull.
- Generates a subsequent electrical field in the brain tissue – which changes brain activity.

- An electrical field in the motor cortex, the part of the brain that makes body parts move, will cause a small twitch in the muscles.
- TMS uses a muscle twitch in the hand to determine the strength of the electric field needed for treatment.

TMS as Treatment

TMS is FDA approved/cleared for:

- Major depression (including with anxiety)
- Obsessive Compulsive Disorder (OCD)
- Smoking Cessation (in Tobacco Use Disorder)

Several companies in the USA:

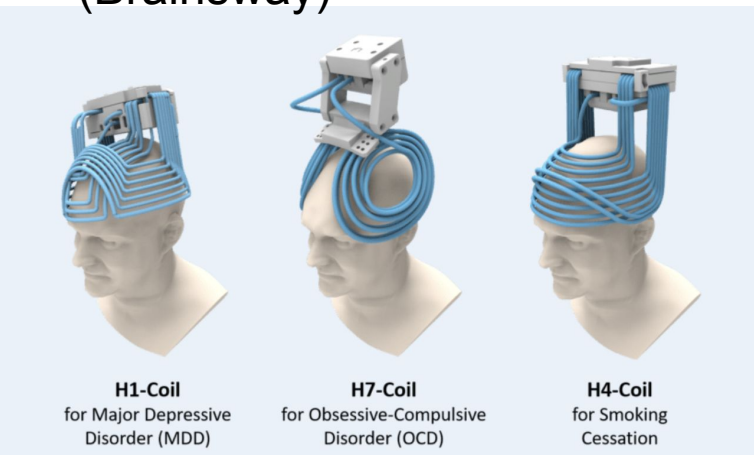
Magstim, Magventure, Soterix, Brainsway, Neuronetics, Neurosoft

Types of coils

Figure 8

Double Cone

H coils (Brainsway)



Types of TMS coils

- Three classes of coils are used for FDA cleared/approved clinical treatment:
  - Figure-of-8 coil (used for MDD)
  - Double cone coil (used for OCD, MDD)
  - H coils: H1 (MDD), H4 (smoking cessation), H7 (OCD, MDD)

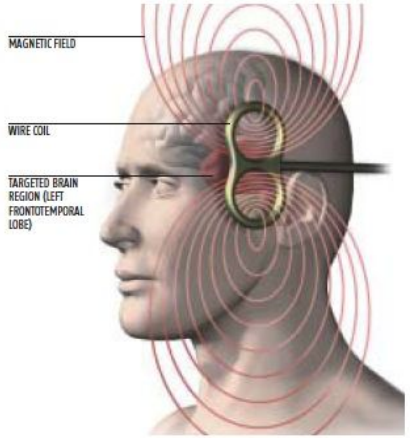
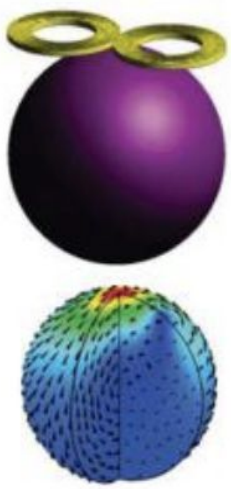
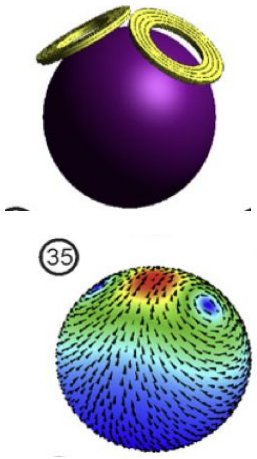
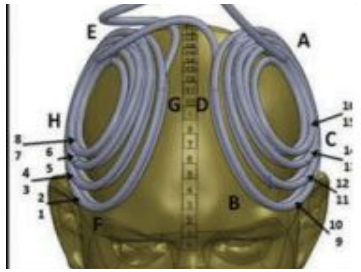


Figure-of-8 coil



Double cone coil



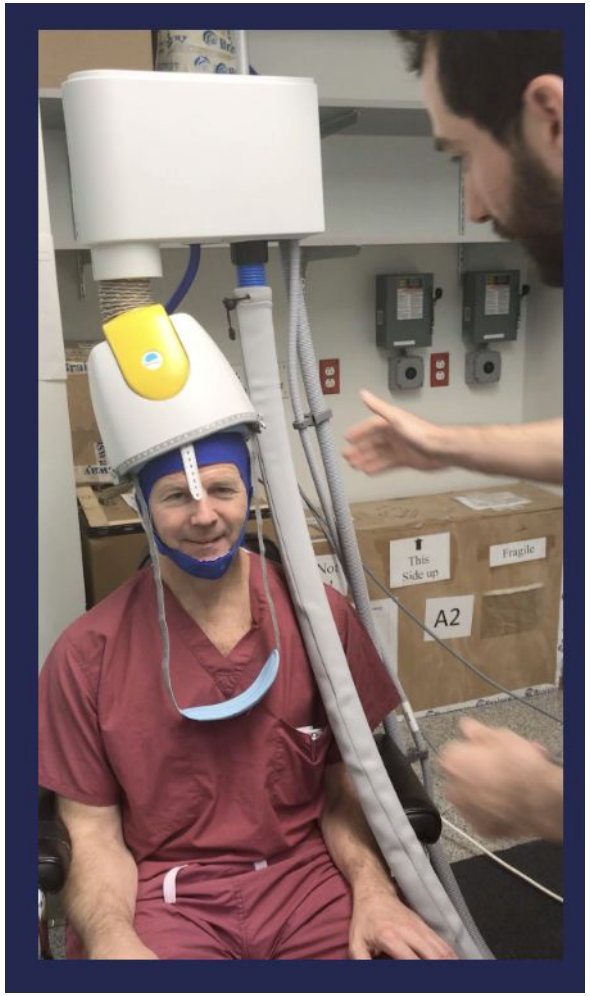


H7 coil

Steps of a TMS Session

- **Resting motor threshold: the intensity of the dose required to elicit motor movement by stimulating the motor cortex (varies across individuals).**
  - Short pulses are delivered to the motor cortex to elicit twitch
  - Treatment is between 80% and 120% of motor threshold
- **Coil is then moved to the brain region being targeted, depending on the diagnosis**
- **The TMS session begins, using these protocols**

- High Frequency (HF), where pulses (about 1800) are delivered over about 30 minutes
- Intermittent theta burst (iTBS), where pulses (about 600) are delivered in about 5 minutes
- Both are equally effective for depression, iTBS is a shorter session



TMS Treatment

- Multiple sessions are needed to improve symptoms: generally 18 to 36 – often given once per day.
- Research with TMS shows that delivery of more than one session per day (accelerated protocols) shorten the time needed to get better. Insurance rarely covers this.

TMS is effective for treatment-resistant depression and OCD

  - For MDD and OCD, about 1/3 reach remission, 50-60% will have a clinical response. TMS usually combined with medication
  - About half stay in remission at six-months (booster sessions can be used).
  - For tobacco use disorder (smoking) about 30% stop smoking

When comparing TMS and ECT for treatment refractory depression, ECT is more effective (higher response rate)

TMS: smoking in tobacco use disorder (TUD)

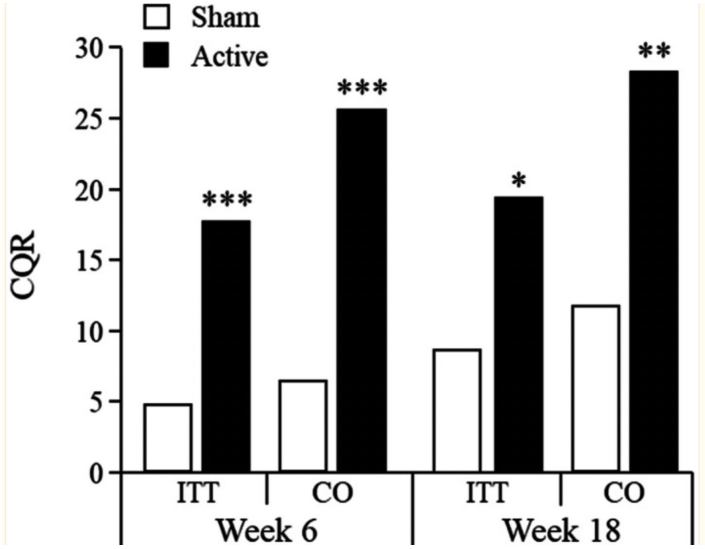
Repetitive transcranial magnetic stimulation for smoking cessation: a pivotal multicenter double-blind randomized controlled trial

Zangen et al, 2021 World Psych

- All participants had TUD and had not been able to quit smoking. TMS delivered with the H4 coil over 6 weeks (total of 18 sessions) using high frequency at 120% of motor threshold.
- The sessions were delivered once per day for 3 weeks, then once per week for three weeks.
- The outcome was continuous quit rate (CQR): 4 weeks of not smo
  The results showed that 17% to 27% of people stopped smoking.

  This is about the same as quit rates seen with medication for TUD (nicotine replacement therapy, varenicline).

  Studies needed that combine TMS with medication for TUD.



TMS: Alcohol Use Disorder (not FDA cleared)

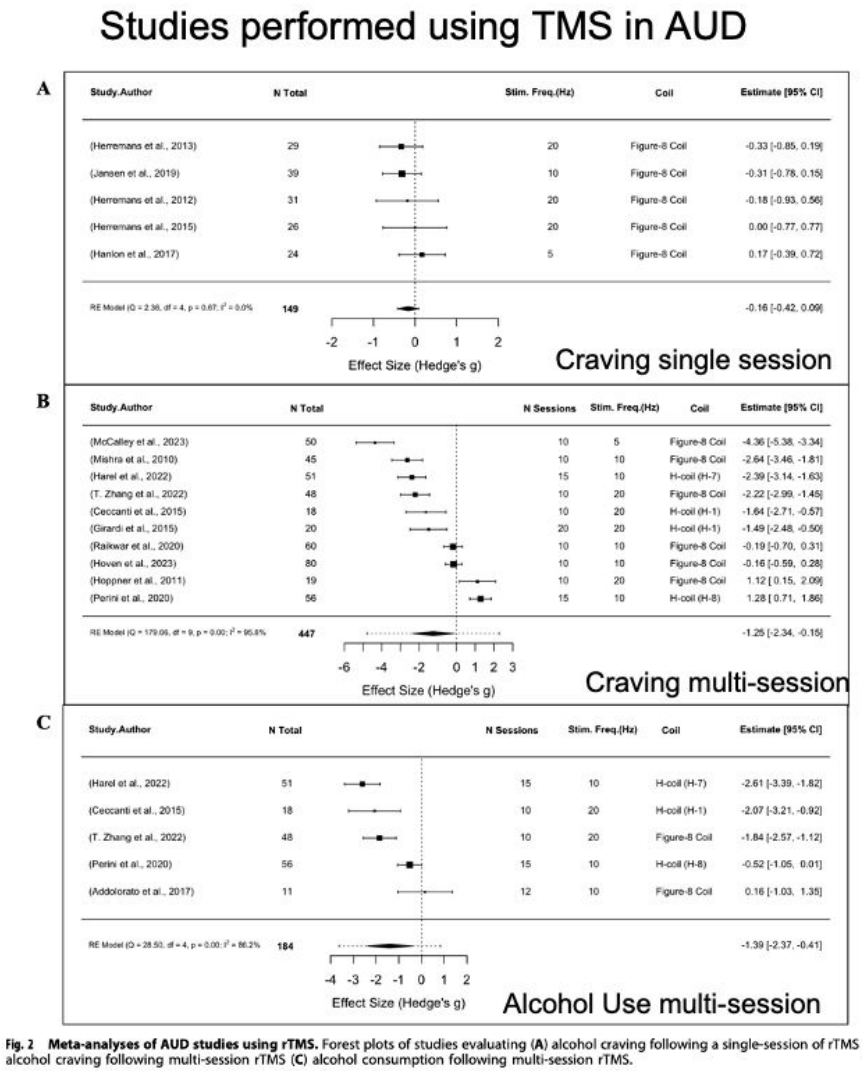


Fig. 2 Meta-analyses of AUD studies using rTMS. Forest plots of studies evaluating (**A**) alcohol craving following a single-session of rTMS (**B**) alcohol craving following multi-session rTMS (**C**) alcohol consumption following multi-session rTMS.

A systematic review and meta-analysis of neuromodulation therapies for substance use disorders

Mehta et al, 2023
Neuropsychopharm

TMS studies in AUD have investigated different coils: Figure 8 and H coils (FDA cleared for depression and OCD)

The meta-analysis showed:

- One sessions of TMS: no effect
- Multiple sessions of TMS: reduced alcohol craving
- Multiple sessions of TMS: reduced alcohol use

There remains a need for a multi-site, large RCT for AUD.

No studies have studies TMS combined with medication for AUD.

TMS: Cocaine/Methamphetamine Use Disorder

Cocaine Use Disorder: multiple studies (> 20) have been conducted using TMS

- Studies used the figure-of-8 coil , H1, and H7 coils (FDA cleared for depression and OCD)
- Many show decreased craving and decreased use.
- However, many of these include low numbers of participants, and some lack sham control.
- **There is a need for a definitive sham-controlled RCT in CUD.**

Methamphetamine Use Disorder:

- Four RCTs, showed improvement in craving following multiple TMS sessions (5–20) with figure 8 coil
- **Need for studies investigating use.**

Not FDA cleared

TMS: Cannabis (marijuana) Use Disorder

Cannabis Use Disorder: shortage of studies, largest RCT by Sahlem et al (2024, Drug Alcohol Dependence)

- Participants (n=72) received active or sham (figure 8 to the L DLPFC) at 120% MT (20 sessions total); follow up for 4 weeks after TMS
- Results showed no effect of craving
- Active group reported fewer days/week of cannabis use versus sham (active: 6 to 4 days/wk versus sham: 6 to 5.1 days/wk)
- No difference in weeks of abstinence between groups

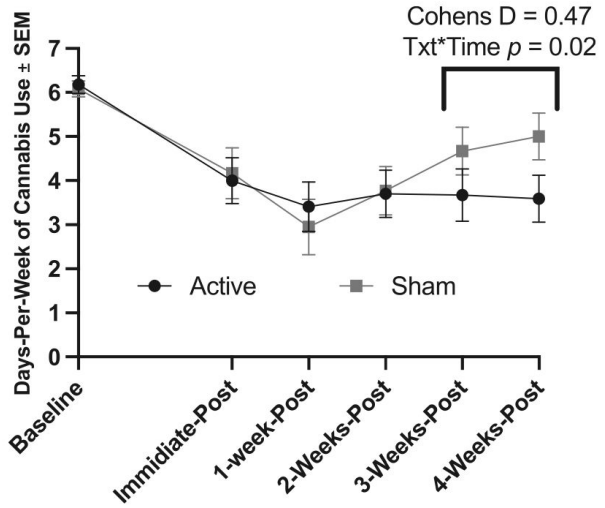


Fig. 3. Days per week of cannabis use: This chart represents the number of days any cannabis was used in the preceding week. Scores are reported with Standard Errors of the Means (±SEM).

TMS for substance use disorders

- TMS is FDA cleared for smoking cessation in tobacco use disorder.
- Promising studies in AUD, showing decreased craving and use, though pivotal RCT needed. *Additional, research combining TMS with medications for AUD needed.*
- Promising studies in cocaine use disorder, including decreased use, multi-site pivotal RCT needed.
- Research needed in cannabis use disorder and methamphetamine use disorder. To date, few studies available.

TMS: side effects and risks

- **Seizure is the most concerning risk**
  - Though not common – meta-analysis (93 RCTs): seizure reported in 0.1 % of participants receiving active TMS and 0.2% in sham group: no significant difference (Zis et al., 2020, Neuromodulation).
- **Hearing Loss (and tinnitus)**
  - Due to noise: prevented with earplugs (patients and operator, make sure fit tight, do not come loose)
- **Headache**
  - Common, tends to improve with number of sessions, usually responds to OTC meds
- **Scalp Pain**
  - Common, tends to improve with number of sessions. Reported in about 30% of patients – for some, TMS cannot be tolerated. Methods used to reduce pain: analgesics, lidocaine, menthol.
  - Greater pain seen with higher motor threshold

TMS: Depression with substance use disorder

Can TMS be used in patients with depression and addiction? **Research is lacking in this patient population**

However:

- Alcohol Use Disorder: most studies (which show promise) use the same coil and target brain region as depression

  Patients with AUD: could be a higher risk of seizure if in withdrawal. Risk expected to be low otherwise

- Cocaine Use Disorder: most studies use the same coil and target brain region as depression

  Patients could be a higher risk of seizure in setting of recent, high dose use (low otherwise)

- Methamphetamine Use Disorder: most studies use the same coil and target brain region as depression

  Studies showed decreased craving, use not measured

- Cannabis Use Disorder: studies show no clear impact on cannabis use – but improvement might be seen in those with comorbid depression (unknown). Risk of seizure expected to be low.

Overall: TMS could improve depression in patients with SUD – caution required in those with AUD and withdrawal, or those with cocaine/methamphetamine use disorder who used recently

TMS: Opioid Use Disorder

TABLE 1. TMS Studies in OUD

Study	n	M:F	Primary Outcome(s)	MOUD	TMS Protocol	Findings
Tsai et al[3] Double-blinded RCT	n = 22 (active—11 and sham—9)	16:4	Opioid craving (VAS) Depressive symptoms (HDRS)	Yes	L. dlPFC 1 session/day for 5 d and then 2 sessions/ week for 3 wk 15 Hz, 100% RMT 2400 pulses/session	Craving decreased with both active and sham TMS Significant decrease in HDRS scores with active TMS compared to sham TMS
Liu et al[4] Double-blinded RCT	n = 112 10 Hz (40) 1 Hz (35) Waitlist controls (37)	112:0	Opioid craving (VAS)	Yes	L. dlPFC 20 sessions over 4 wk 10 Hz, 100% RMT 2000 pulses/sessions 1 Hz, 100% RMT, 600 pulses/session	Significant reduction in craving with 10 and 1 Hz compared to waitlist controls
Kang et al[5] Double-blinded RCT	n = 42 (active—20 and sham—22)	42:0	Opioid craving (VAS)	Yes	L. dlPFC 3 sessions/day for 10 d iTBS, 80% RMT 600 pulses/session	Significant reduction in craving with iTBS compared to sham iTBS
Shen et al[6] RCT	n = 20 (active—10 and sham—10)	20:0	Opioid craving (VAS)	Yes	L. dlPFC 1 session/day for 5 d 10 Hz, 100% RMT 2000 pulses/session	Significant decrease in craving on VAS after 5 d of active TMS compared to sham TMS
Li et al[8] Retrospective chart review unknown	n = 100 (50 received TMS, 50 did not)	75:25	Opioid craving (VAS) Depressive symptoms (SDS) Anxiety Symptoms (SAS)	Unknown	L. dlPFC 1 session/day for 5 d, 8 wk 20 Hz, 100% MT	Significant decrease in opioid craving, and depressive and anxiety symptoms after active TMS compared to sham TMS

Owen et al, 2024 Journal of ECT

<u>TMS studies OUD:</u>

Four randomized controlled trials (1 retrospective)

All targeted L DLPFC (fig 8); stimulation parameters ranged:1 – 20 Hz and intermittent theta burst stimulation (iTBS).

All 4 RCTs showed a decrease in opioid craving with TMS compared to sham.

Two studies, including 1 RCT and a retrospective review, showed a significant decrease in depressive symptoms compared to sham, in addition to opioid craving.

Focused Ultrasound as an Adjunctive Treatment Approach for Substance Use Disorder

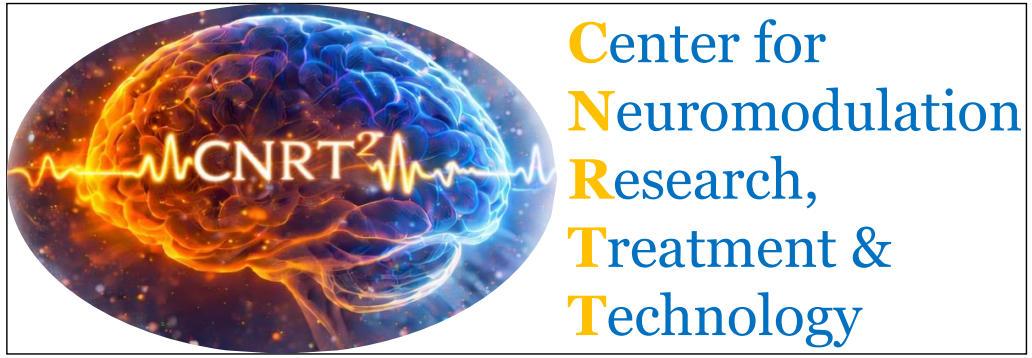
James J. Mahoney, PhD

Associate Professor and Clinical Neuropsychologist

Director, Center for Neuromodulation Research, Treatment & Technology

University of Virginia School of Medicine

Department of Psychiatry and Neurobehavioral Sciences



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Center for Neuromodulation Research, Treatment & Technology

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Presentation Outline

- Forms of Neuromodulation and Approaches
- Brain Targets
- Focused Ultrasound (FUS) – Background/Procedures
- Early FUS Findings and Results from Addiction Trials
- FUS Future Directions

Substance Use Disorder (SUD) Crisis in the United States

- ~48.4 million people had a SUD diagnosis in 2024 (NSDUH, 2025)

- Rates of relapse and recurrent drug use remain elevated
  - After completing 28-day residential program, up to **75% relapse** in the initial weeks after discharge (CDC, 2024; Nunes 2018)

- Most non-opioid substances, such as methamphetamine and cocaine, do not yet have medication treatments available (Mahoney, 2021)

Neuromodulation has the potential to reduce those risk factors associated with relapse, such as craving and emotional distress

Neuromodulation Approaches for Addiction

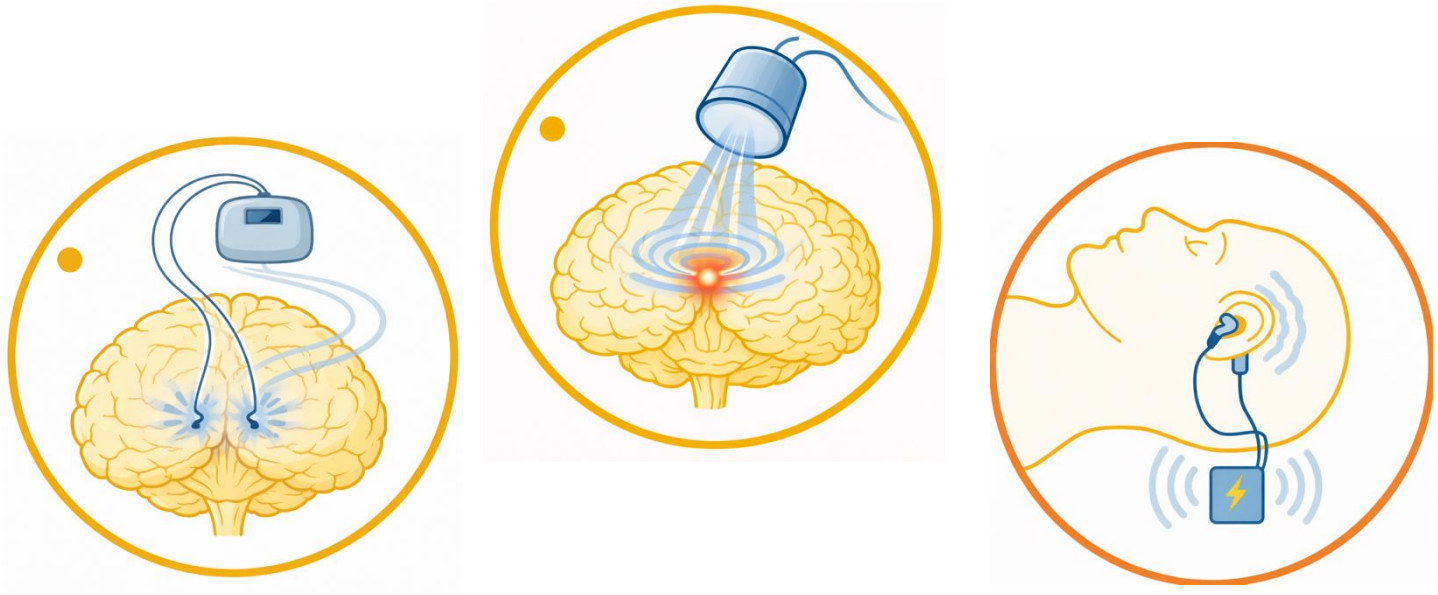
Transcranial Magnetic Stimulation (TMS)

Top-Down Neuromodulation

Inhibitory Control, Decision Making, Planning, Behavioral Self-Regulation

Deep Brain Stimulation (DBS);

Focused Ultrasound (FUS); Vagus Nerve Stimulation (VNS)



Bottom-Up Neuromodulation

Reward, Emotions, Behavioral Regulation, Disinhibition, Attention, Craving, Habit Formation

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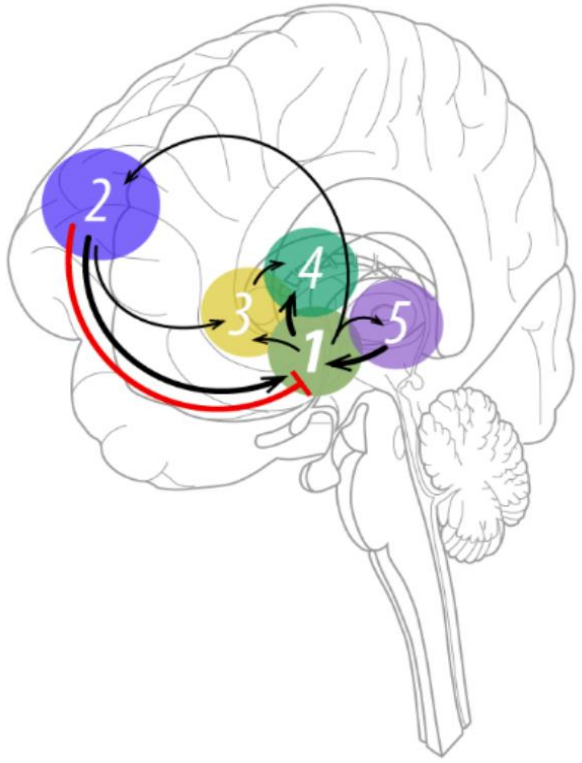
Nucleus Accumbens (NAc) Target for Addiction

- Multiple regions associated with addiction and reward

  Nucleus Accumbens (NAc), Insula, Prefrontal Cortex, etc.

- NAc dysfunction and dysregulation plays a key role in addiction

- NAc is an integral part of the reward circuitry which maintains both direct and indirect connections with the PFC, insula, ACC, dorsal striatum, and amygdala



1 NAc
Reward

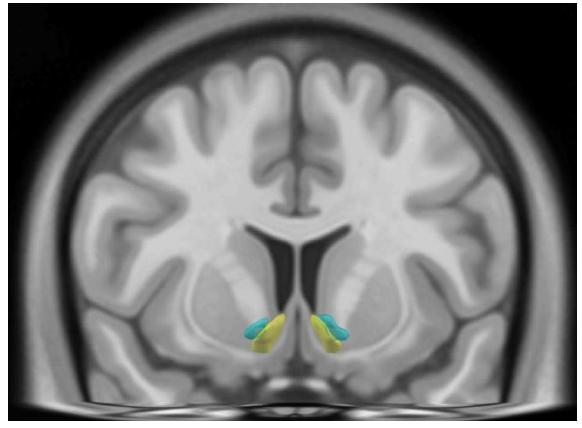
2 PFC
Inhibitory control, decision-making, planning, conditioning, salience attribution

3 Insula ACC
Introspection

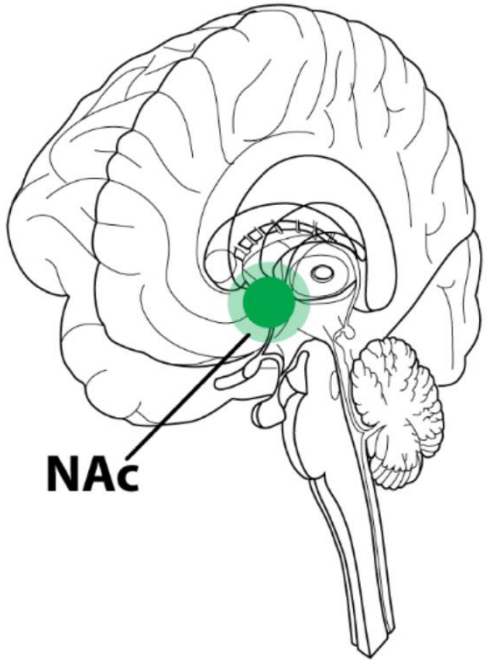
4 Dorsal striatum
Habits, drive, action

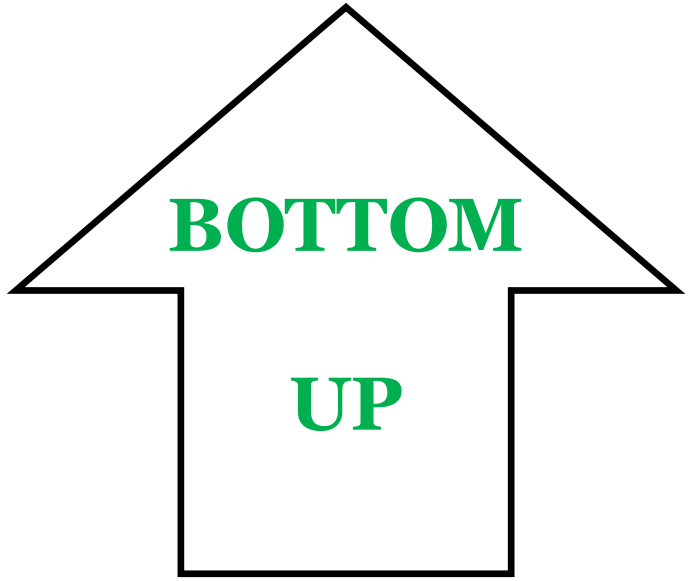
5 Amygdala hippocampus
Stress reactivity, mood, conditioning

Adapted from: Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010; 35(1): 217-38.



Neuromodulation – Bottom-Up Approach





Target the Nucleus Accumbens (NAc)

Focused Ultrasound

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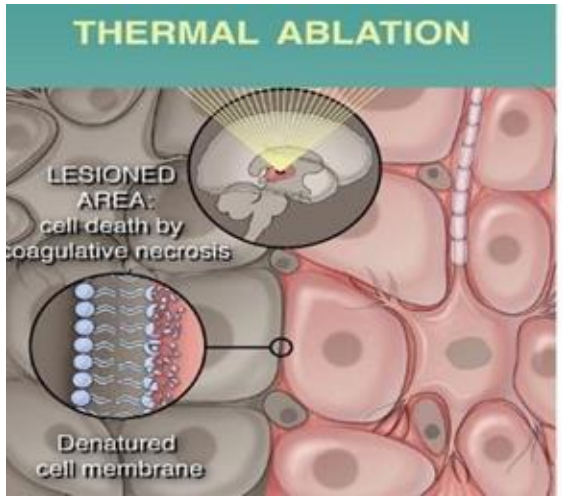
Focused Ultrasound from Diagnostic to Brain Therapeutics

Diagnostic Ultrasound
Frequency 1-20 MHz
<1 W/CM² ISPTA

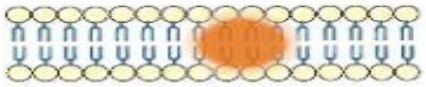
Imaging

High Intensity FUS
Frequency .5-4 MHz
10-1000 W/CM² ISPTA



Tremor
Parkinson's disease
Epilepsy
Neuropathic pain
Obsessive compulsive disorder
Depression

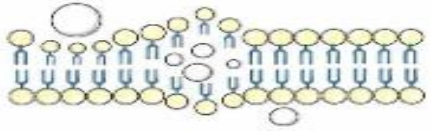
Heat



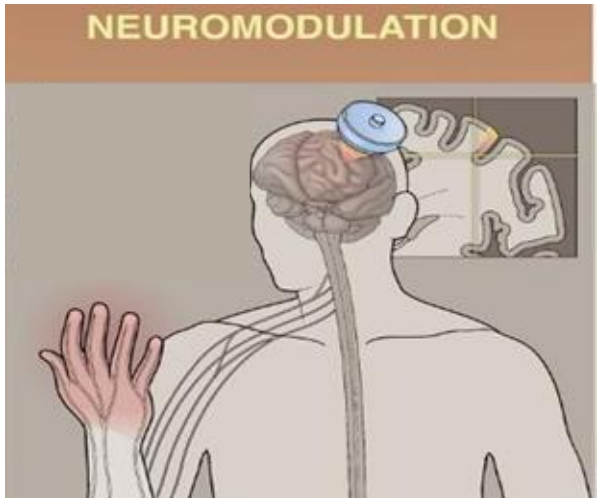
FUS Blood Brain Barrier opening
Frequency 200-700 kHz
1-5 W/CM² ISPTA

Targeted Therapeutic Delivery
Brain Tumors
Alzheimer's Disease
Parkinson's Disease., ALS

Cavitation

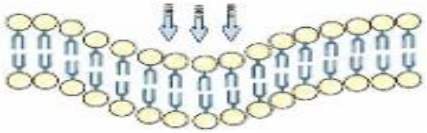


FUS Neuromodulation
Frequency 200-700 kHz
1-5 W/CM² ISPTA



Addiction
Anxiety, Depression, PTSD
Chronic pain
Dementia

Mechanical force



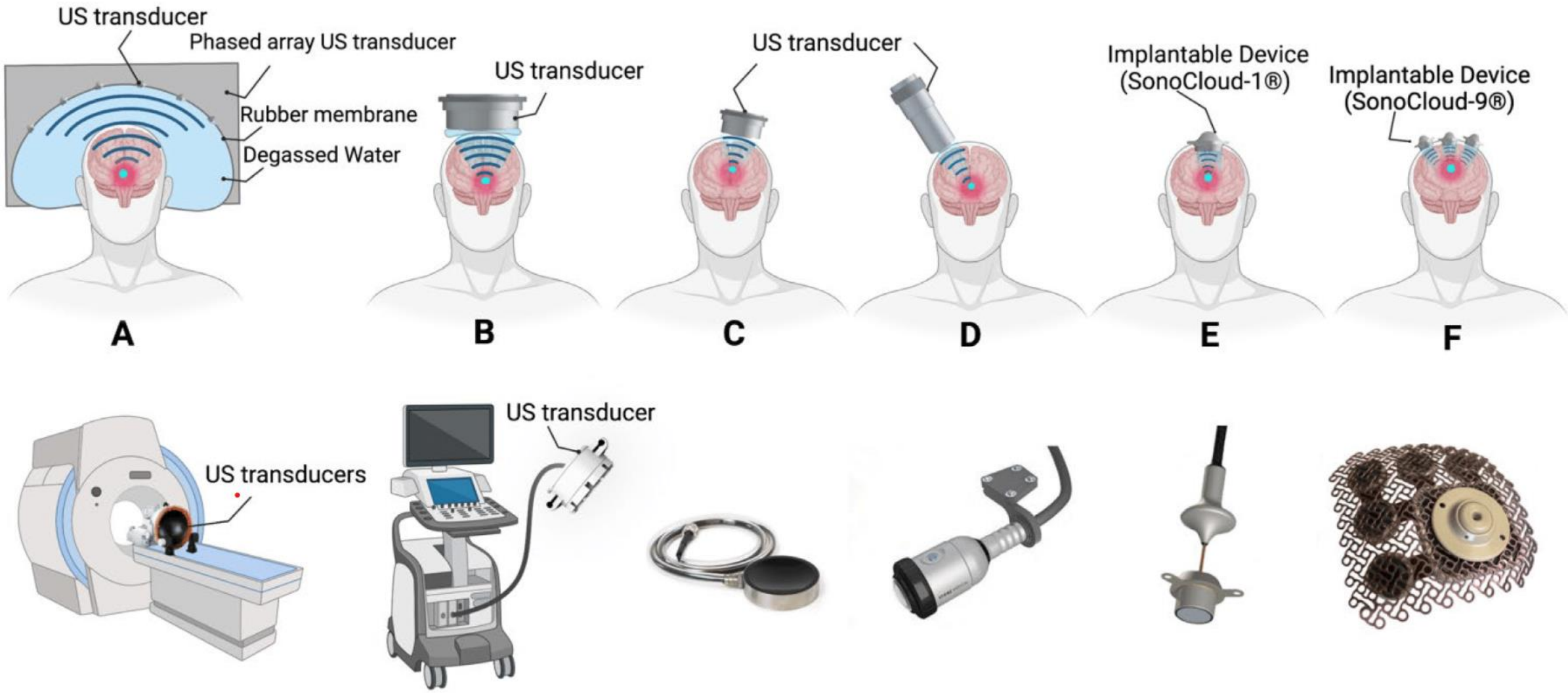

JAMA Neurology | Review JAMA Neurol. 2018;75(2):246-254

A Review of the Current Therapies, Challenges, and Future Directions of Transcranial Focused Ultrasound Technology

Advances in Diagnosis and Treatment

Vibhor Krishna, MD, SM; Francesco Sammartino, MD; Ali Rezai, MD

Focused Ultrasound (FUS) Devices



Barzagar-Fallah et al. Pharmaceutics, 2022

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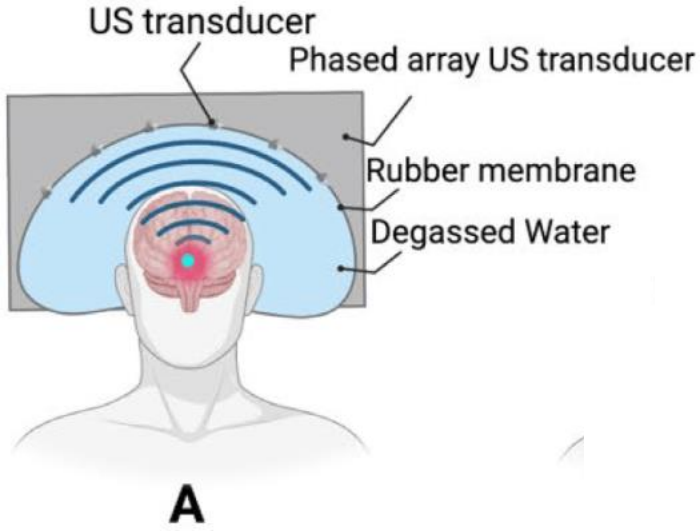
Focused Ultrasound (FUS) Devices



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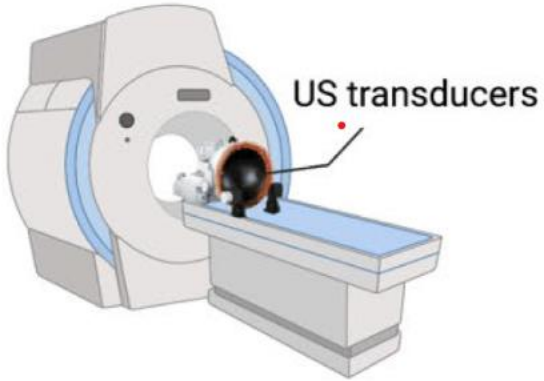

Insightec ExAblate System

Barzagar-Fallah et al. Pharmaceutics, 2022

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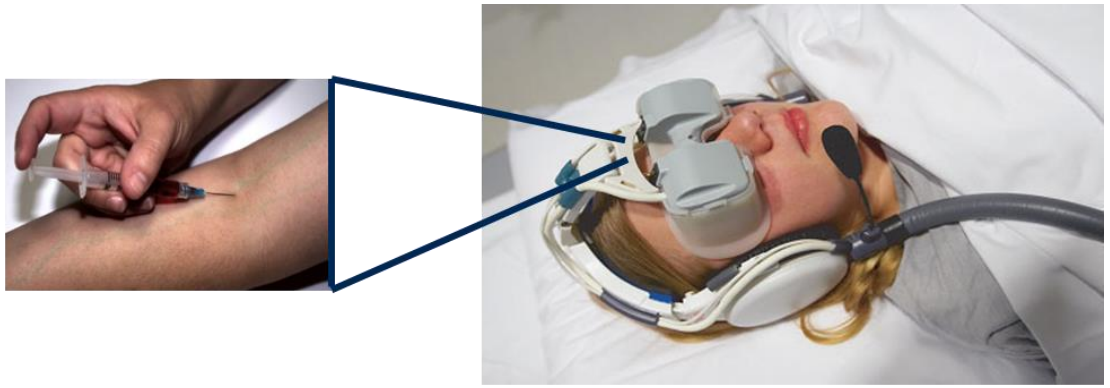
Focused Ultrasound Procedure

- ~1-2 hour treatment including set-up
- Stereotactic frame
- Live feedback via personalized visual cue induced craving throughout session



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FUS for SUD Open-Label Clinical Trial – Participants and Objectives

Study 1: 2021

- **4** participants (Primary OUD), Unilateral FUS of the NAc
  - 2 participants received a Low FUS dose (60W)
  - 2 participants received *Enhanced/Therapeutic* dose (90W)

Clinicaltrials.gov ID#: NCT04197921 **IDE#**: G190092 (Insightec)

frontiers | Frontiers in Psychiatry
TYPE Original Research
PUBLISHED 15 September 2023
DOI 10.3389/fpsyt.2023.1211566

Low-intensity focused ultrasound targeting the nucleus accumbens as a potential treatment for substance use disorder: safety and feasibility clinical trial

James J. Mahoney[1,2*], Marc W. Haut[1,2,3], Jeffrey Carpenter[2,4], Manish Ranjan[5], Daisy G. Y. Thompson-Lake[2], Jennifer L. Marton[1,2], Wanhong Zheng[1,2], James H. Berry[1,2], Padma Tirumalai[2], Ashley Mears[5], Pierre D'Haese[2], Victor S. Finomore[2], Sally L. Hodder[6] and Ali R. Rezai[2,5]

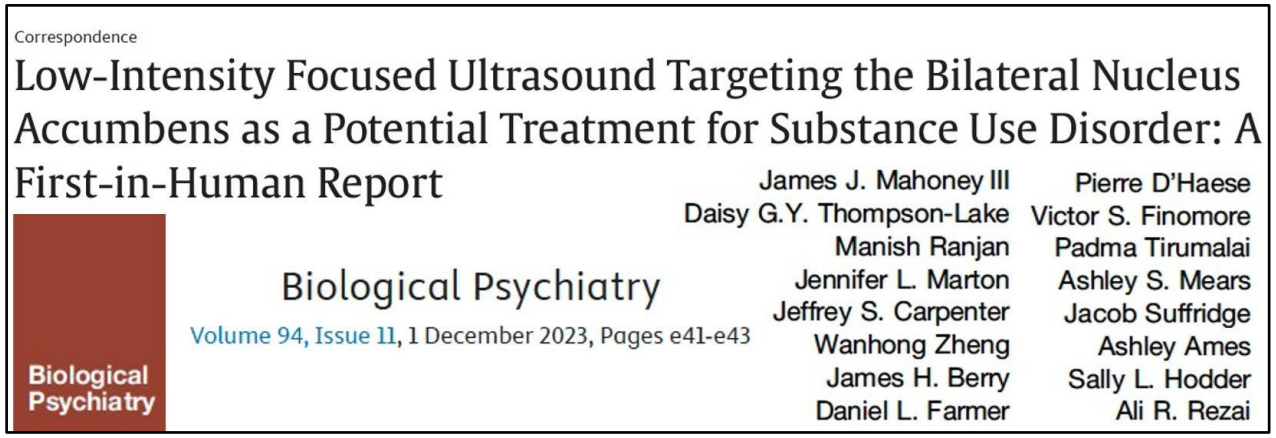
- Primary Objective – Investigate safety and tolerability of FUS targeting the NAc in participants with OUD and co-occurring SUDs at 90 days post-FUS

- Secondary Objective – Assess the effects of FUS on substance craving at 90 days post-FUS

FUS for SUD Open-Label Clinical Trial – Participants

Study 2: 2022 – 2024

- **16** participants, **Bilateral/Simultaneous** NAc FUS with *Therapeutic* dose (90-100W)
  - **14** participants w/ Primary OUD
    - **8** have completed the study (Biological Psychiatry)
  - **1** participant w/ Primary Meth Use Disorder
  - **1** participant w/ Primary Alcohol Use Disorder



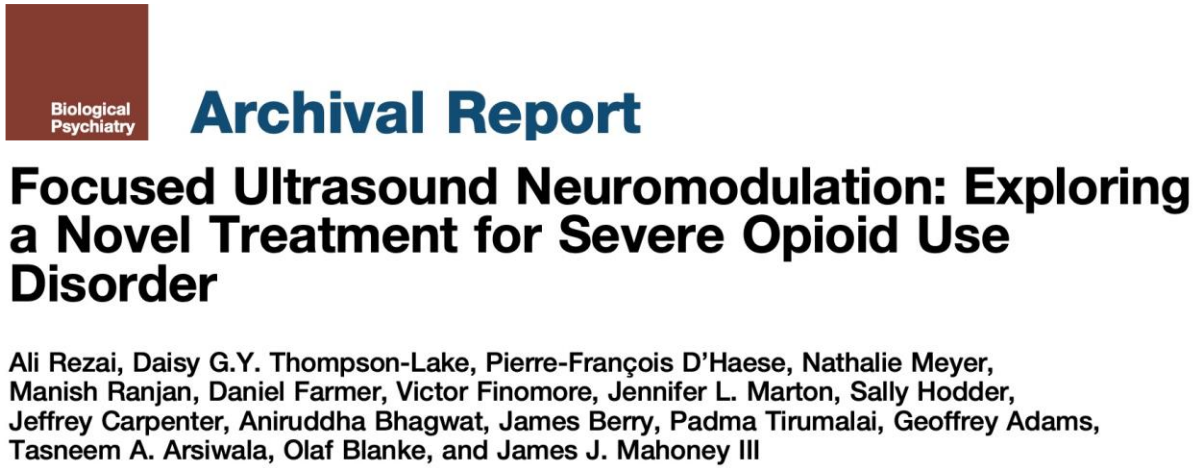
Correspondence

Low-Intensity Focused Ultrasound Targeting the Bilateral Nucleus Accumbens as a Potential Treatment for Substance Use Disorder: A First-in-Human Report

James J. Mahoney III, Daisy G.Y. Thompson-Lake, Manish Ranjan, Jennifer L. Marton, Jeffrey S. Carpenter, Wanhong Zheng, James H. Berry, Daniel L. Farmer, Pierre D'Haese, Victor S. Finomore, Padma Tirumalai, Ashley S. Mears, Jacob Suffridge, Ashley Ames, Sally L. Hodder, Ali R. Rezai

Biological Psychiatry

Volume 94, Issue 11, 1 December 2023, Pages e41-e43



Biological Psychiatry

Archival Report

Focused Ultrasound Neuromodulation: Exploring a Novel Treatment for Severe Opioid Use Disorder

Ali Rezai, Daisy G.Y. Thompson-Lake, Pierre-François D'Haese, Nathalie Meyer, Manish Ranjan, Daniel Farmer, Victor Finomore, Jennifer L. Marton, Sally Hodder, Jeffrey Carpenter, Aniruddha Bhagwat, James Berry, Padma Tirumalai, Geoffrey Adams, Tasneem A. Arsiwala, Olaf Blanke, and James J. Mahoney III

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Bilateral NAc Focused Ultrasound for SUD

Recruitment Population

Eligibility Criteria

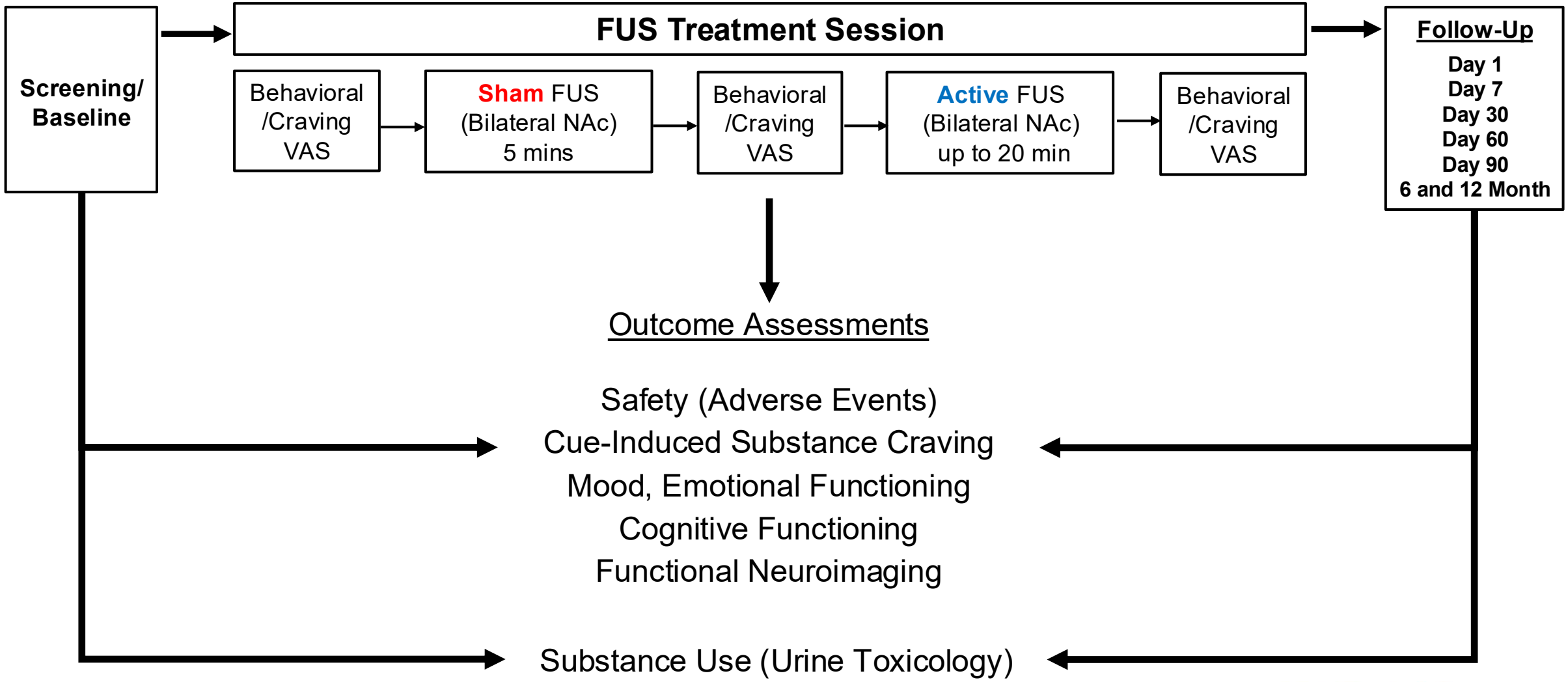
- Patients recruited from a residential 28-day treatment program
- Primary Opioid Use Disorder (can have co-occurring SUDs)
- Compliant with medication for OUD (MOUD) for at least 1 week prior to enrollment

Clinicaltrials.gov ID#: NCT04197921; IDE#: G190092 (Insightec)

NIDA: DA047714-04S1

Bilateral FUS for SUD

Open-Label Study Design



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FUS for SUD Open Label Trial - Participant Characteristics

	N = 8
Age (years)	35.5 [23 – 48]
Sex	6 male/2 female
# of Overdoses *(n=6)*	4 [1 – 5+]
Prior Treatment Attempts	4 [3 – 10+]
Opioid Use Characteristics	
Specific Opioids Used	Heroin, Fentanyl, Hydro/Oxycodone
Heroin/Fentanyl	
Years of Use	14.1 [4 – 36]
Primary Route of Use	3 (IV); 5 (Smoke)
Prescription Opioids	
Years of Use	14.9 [1-37]
Primary Route of Use	1 (IV); 2 (Smoke); 4 (Nasal); 1 (Oral)
Values represent Median [range]	

Non-Opioid Substance Use Characteristics	
Years of Use	
Methamphetamine *(n=8)*	9 [1 – 26]
Cocaine *(n=6)*	19 [3 – 36]
Benzodiazepines *(n=6)*	18.5 [1 – 34]
Alcohol *(n=8)*	23.5 [9 – 38]
Cannabis *(n=8)*	21.5 [11 – 37]
Nicotine *(n=8)*	20.5 [9 – 38]
Values represent Median [range]	

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Open-Label FUS-SUD Pilot Trial

Safety and Tolerability Outcomes

Assessed during FUS procedure and Post-FUS Follow-Up

Open-Label FUS-SUD Pilot Trial
Safety and Tolerability

- Safe and well-tolerated – no unexpected AEs or FUS procedure related SAEs
- No adverse structural brain changes on multiple MRI sequences immediately post-FUS & follow-up

Behavioral and Functional Outcomes:

- No adverse reductions in naturally reinforcing (e.g., eating) and pleasurable behaviors or any other indicators of NAc dysfunction post-FUS
  - Snaith Hamilton Pleasure Scale (SHAPS) and Neuro-Quality of Life Subscales:
    - Satisfaction with Social Roles and Activities
    - Positive Affect and Well-Being
    - Ability to Participate in Social Roles and Activities

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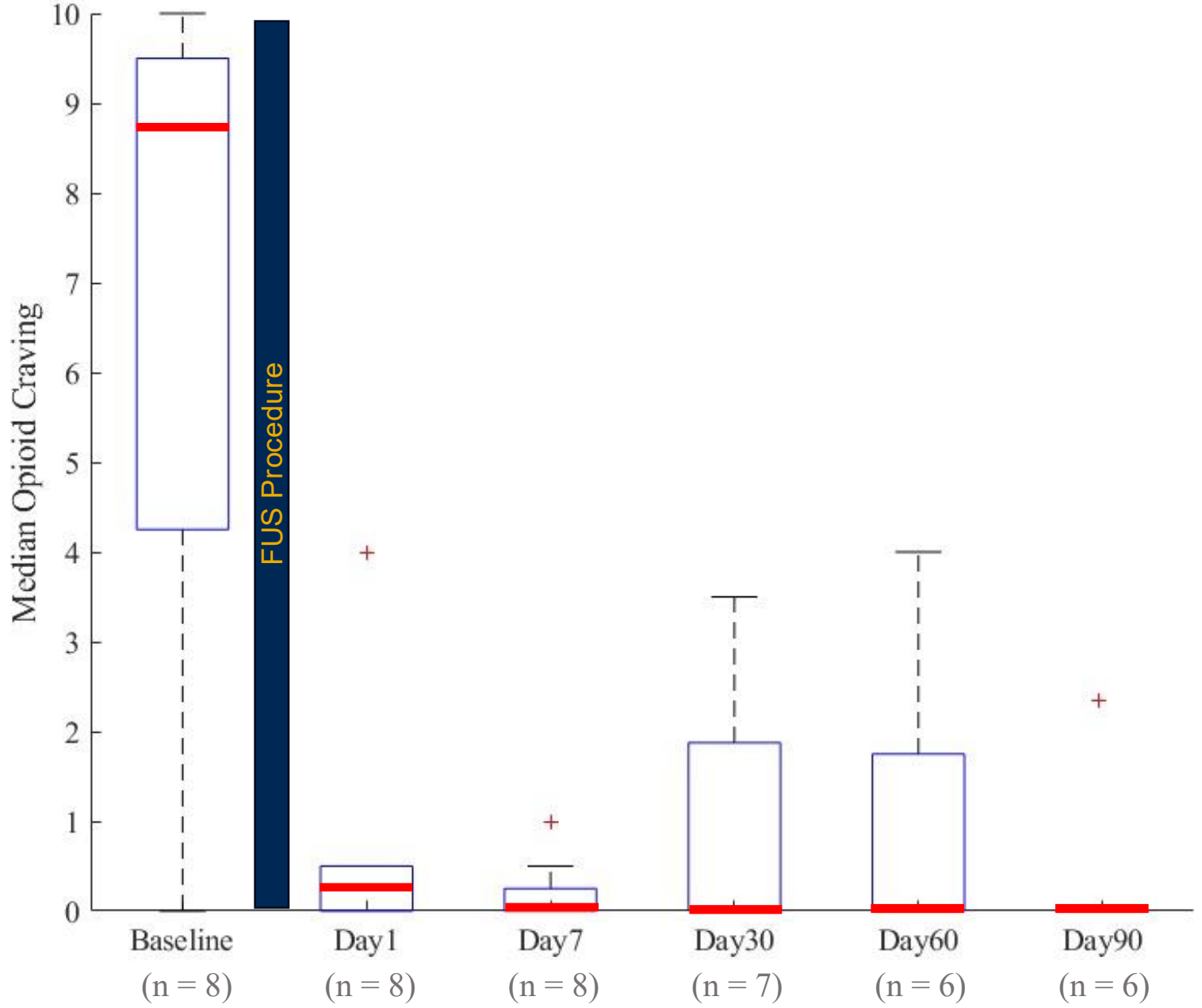
Cue-Induced Craving Outcomes

Pre-FUS Baseline Versus Post-FUS Follow-Up

Opioid Craving at Baseline Vs. Post FUS Follow-Up



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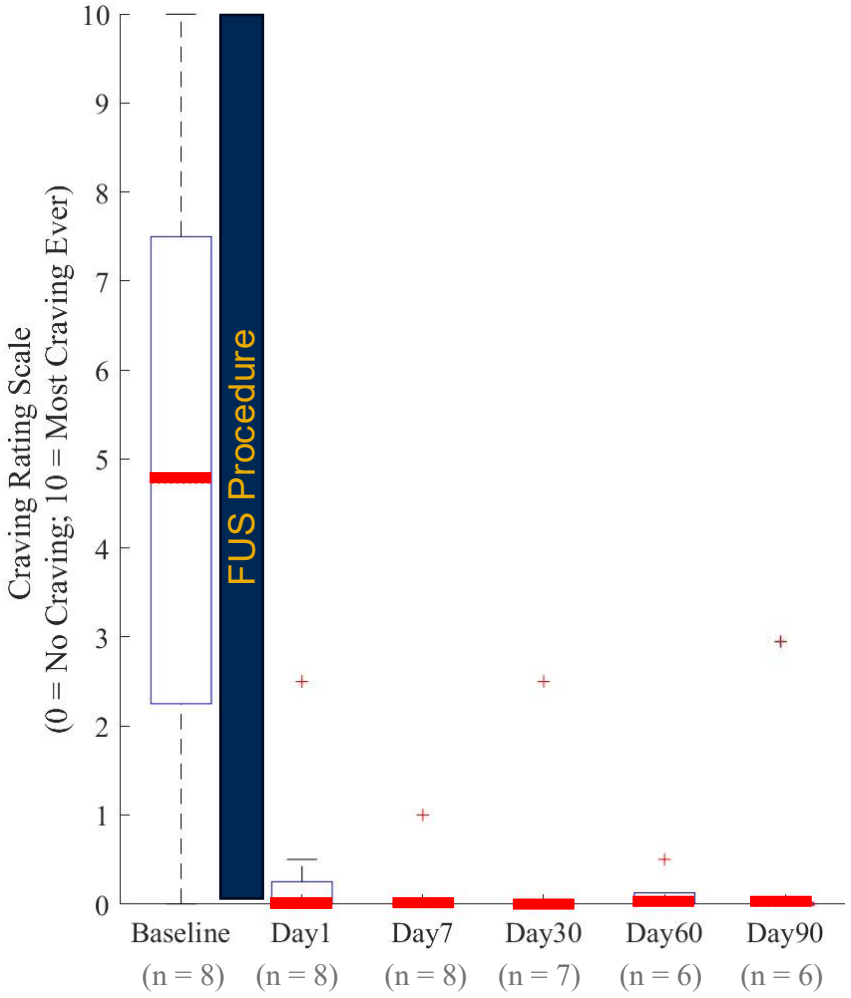
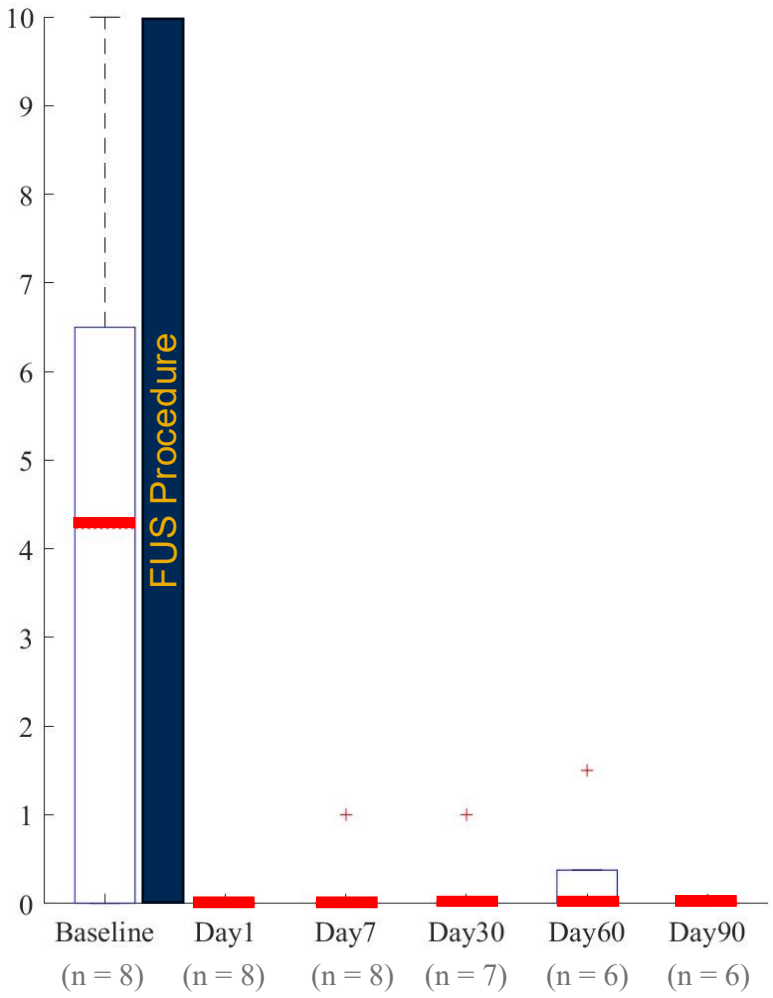
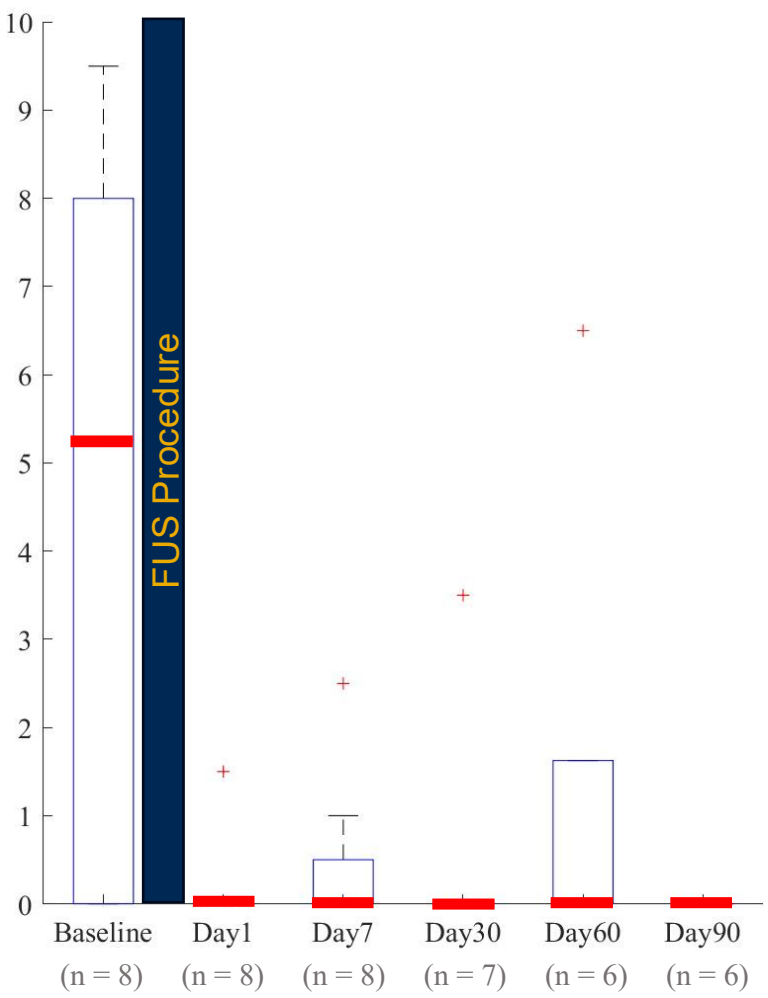
Non-Opioid Craving at Baseline Vs. Post FUS Follow-Up



Methamphetamine



Cocaine



Benzodiazepines

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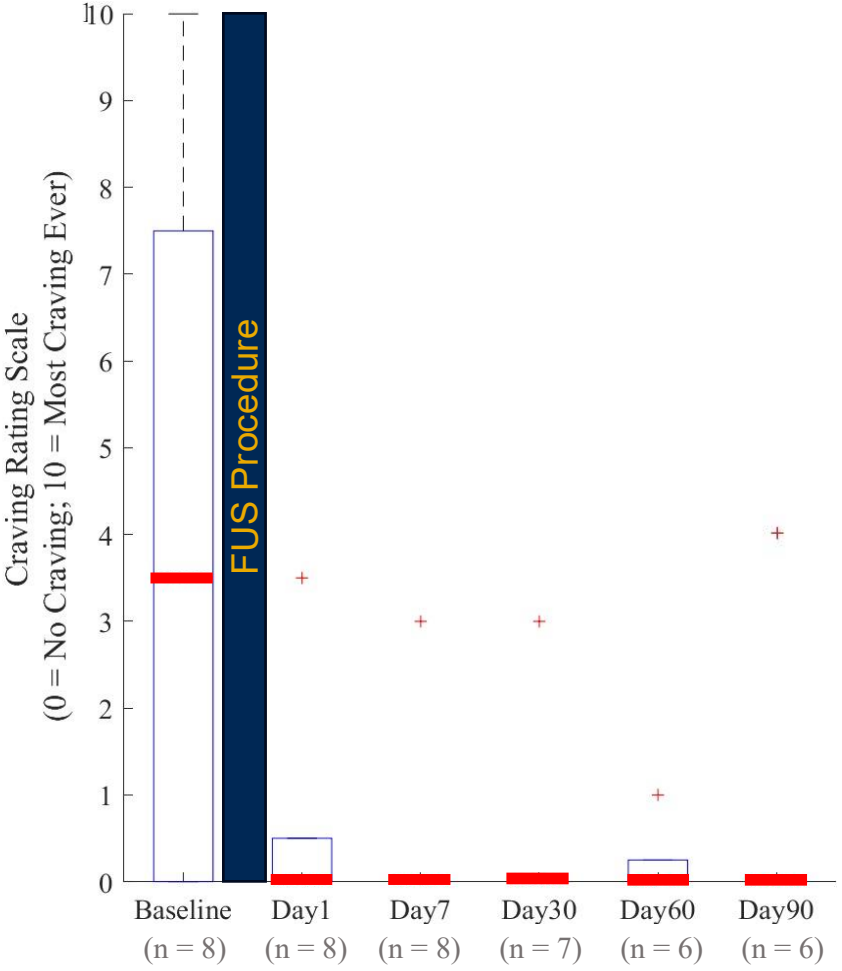
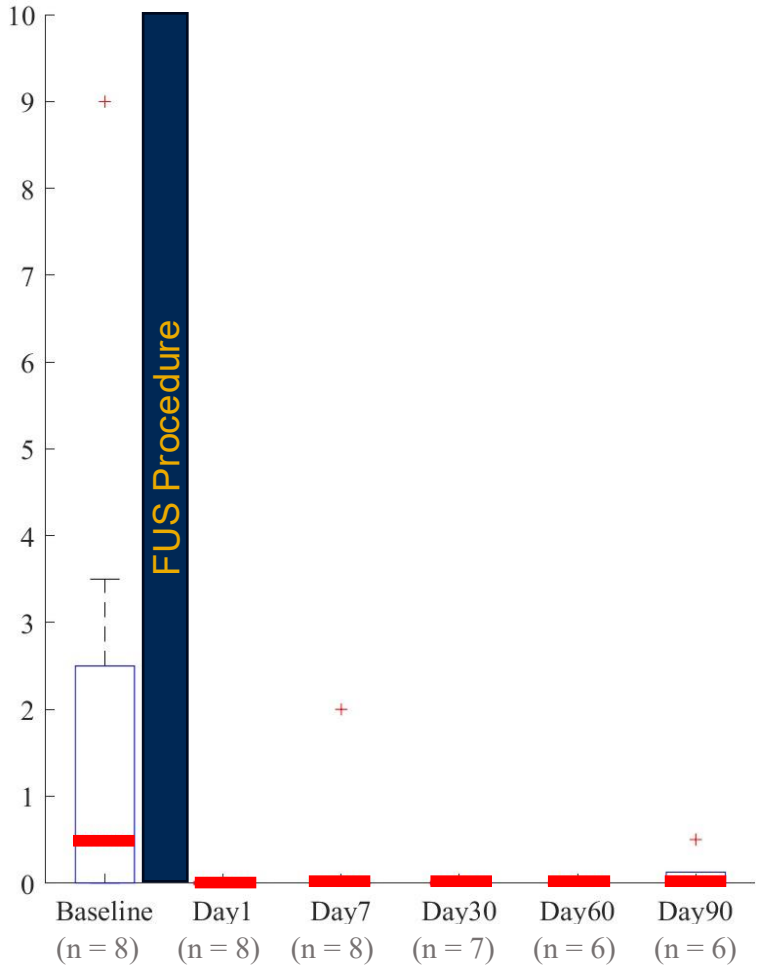
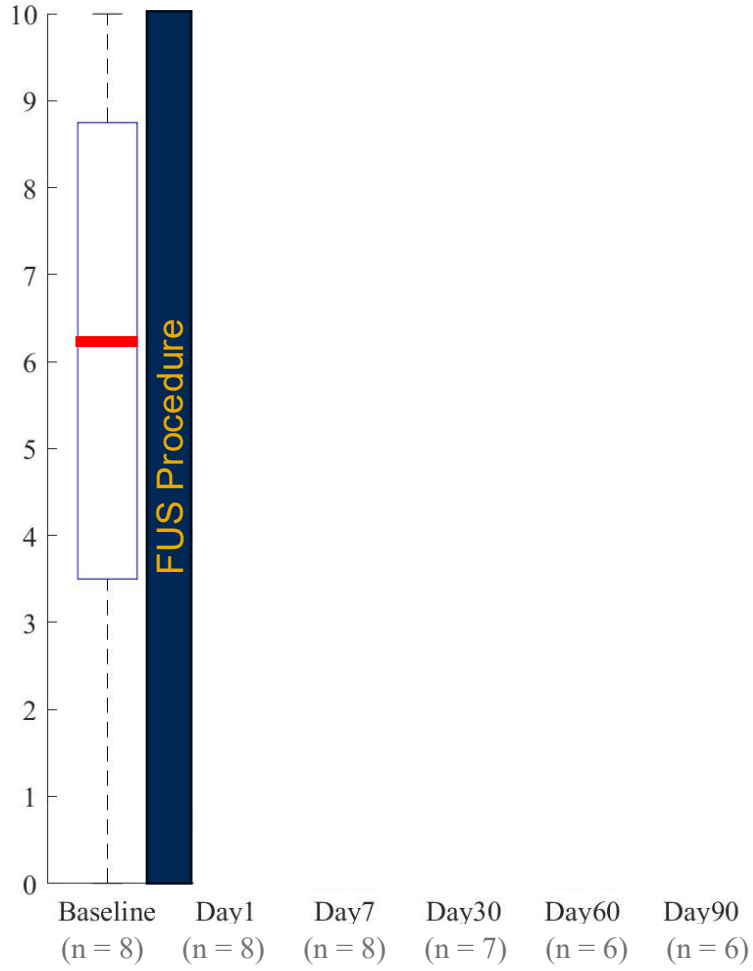
Non-Opioid Craving at Baseline Vs. Post FUS Follow-Up



Cannabis



Alcohol



Nicotine

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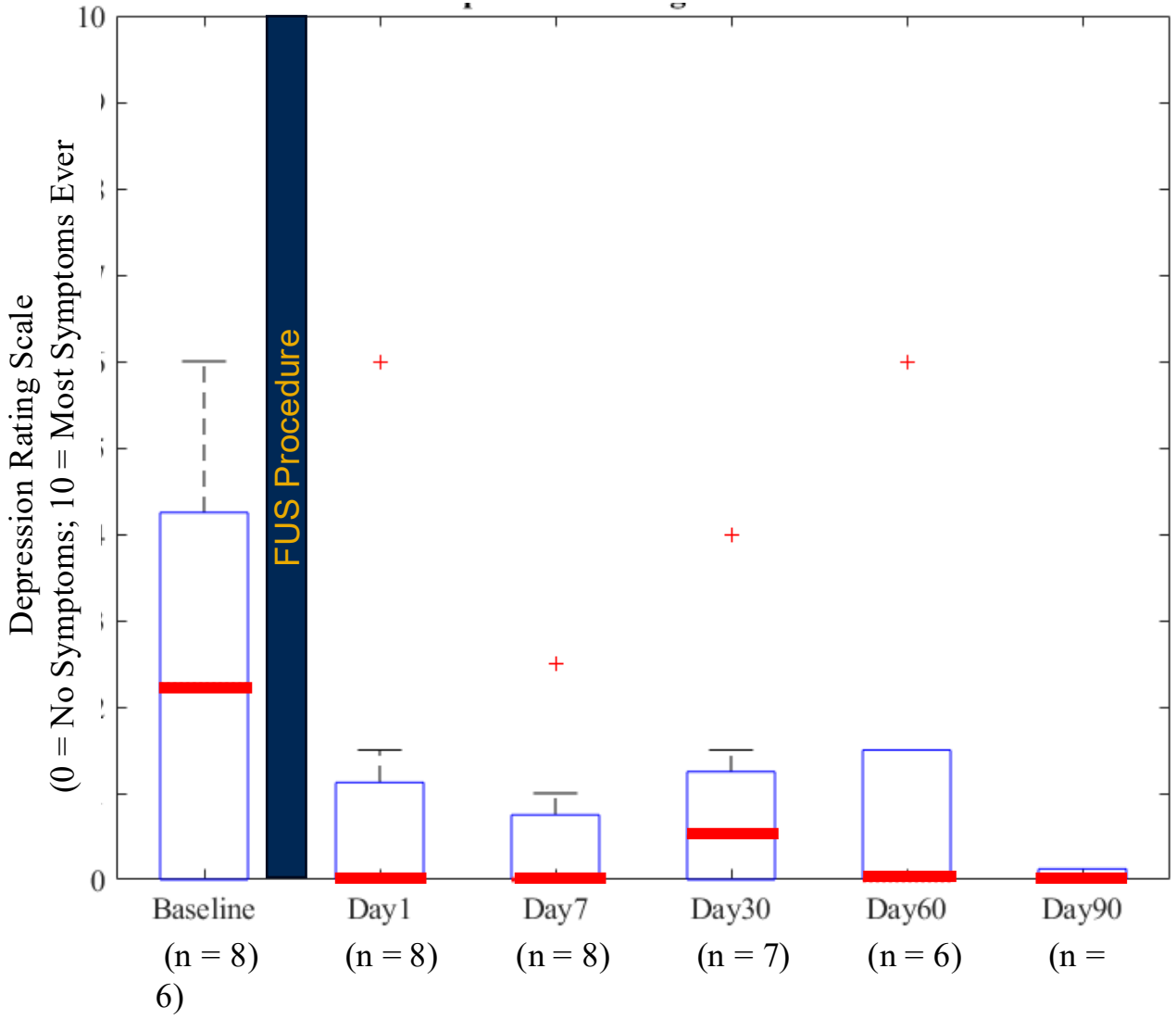
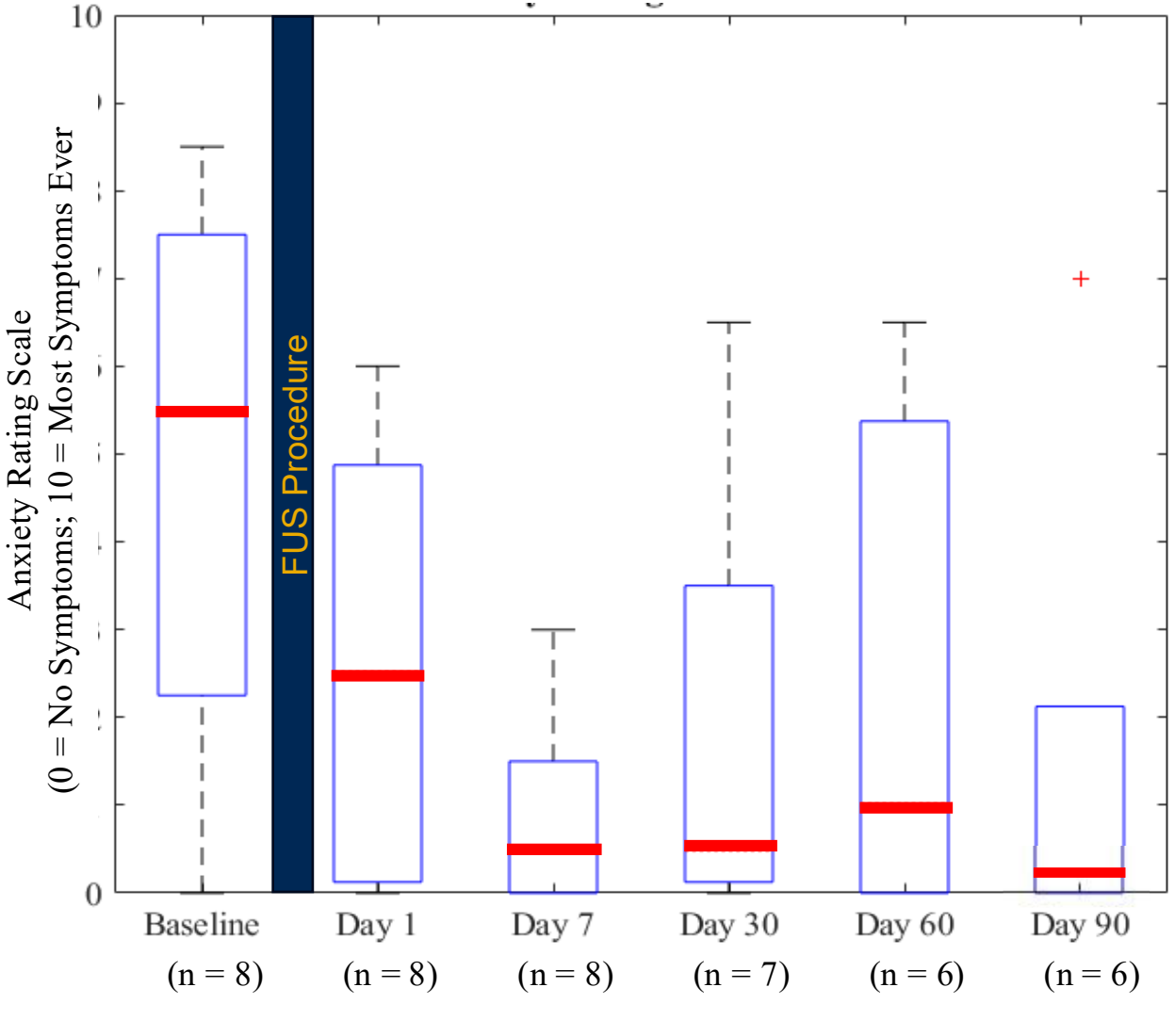
Emotional Outcomes (Depression and Anxiety)

Pre-FUS Baseline Versus Post-FUS Follow-Up

Depression and Anxiety at Baseline Vs. Post FUS Follow-Up





Depression

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Anxiety

Substance Use Outcomes

Pre-FUS Baseline Versus Post-FUS Follow-Up

Bilateral FUS for Primary OUD

Urine Toxicology Results at Post-FUS Follow-Up

Participant	Post-FUS Follow-Up Day				
	1	7	30	60	90
1	–	–	–	–	–
2	–	–	–	–	–
3	–	–	+ (fent, opi)	–	–
4	–	–	–	+ (fent)	–
5	–	–	–	–	–
6	–	–	–	+ (fent)*	
7	–	–	–	–	–
8	–	–	–	–	--

– : Negative for all substance on quantitative urine toxicology

+ : Positive for the following substances on quantitative urine toxicology - Fentanyl (Fent), Opiates (Opi),

*Participant #6 had relapse at day 60 follow-up and underwent a 2nd FUS treatment following drug use recurrence.

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Open-Label FUS-SUD Pilot Trial

Functional MRI Connectivity Outcomes

Resting State Functional MRI Bilateral NAc to the Rest of the Brain

Changes in Connectivity Pre- and Post-FUS

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Functional Resting State Contrast Analysis

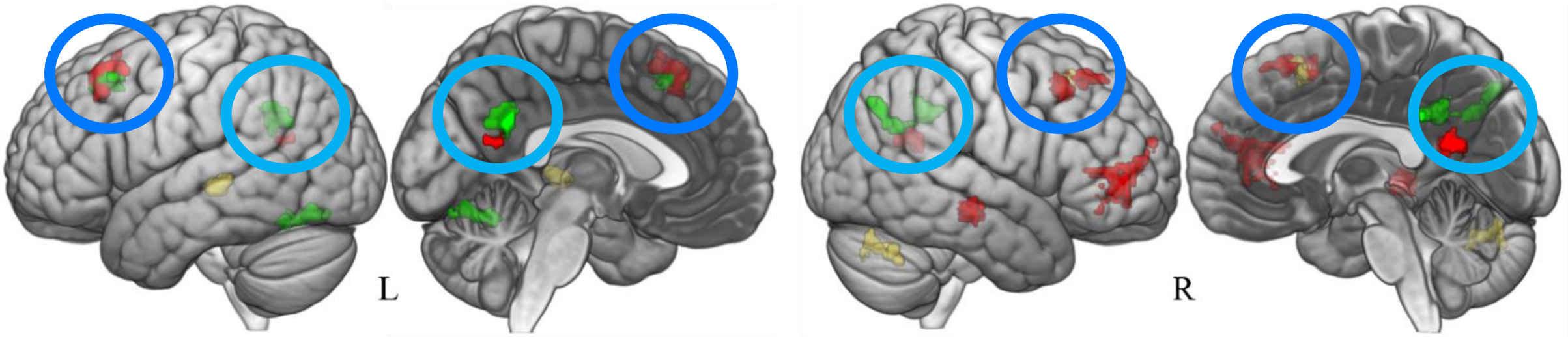
Results: Reduced Positive Connectivity Following FUS in the:

- Dorsolateral Prefrontal Cortex (DLPFC)
- Posterior Cingulate Cortex (PCC)

Day 7 (n=8)

Day 30 (n=7)

Day 90 (n=5)



Rezai, Thompson-Lake, Mahoney et al, Biological Psychiatry (2025)

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Behavioral and Functional Changes Post-FUS

Craving Reduction

- Significant decrease in cravings in familiar settings
- Difficulty "connecting" to the cues which would normally induce craving and use
- Reduced thoughts and dreams related to drugs or alcohol

Enhanced Mood/Functioning

- **Stable Desires**: No change in pleasure (e.g., food).
- **Enhanced Mood:** Improved anxiety, frustration tolerance, and reduced irritability.
- **Sharper Focus**: Boosted motivation, clearer thinking, and more goal-driven.
- **Life Engagement:** More involved in family, work, and education.

FUS Neuromodulation for Addiction
Open-Label Pilot Trial Summary

- 20 patients total with severe substance use disorder
  - Multiple inpatient, 28-day residential, outpatient treatments
  - Numerous overdoses
- 20-minute focused ultrasound treatment
- Safe and feasible
- Significantly reduced drug craving and substance use
  - Opioid, benzo, cocaine, methamphetamine, alcohol
- Long term sustainability (1 year)

Clinicaltrials.gov ID#: NCT04197921

IDE#: G190092 **NIDA: DA047714-04S1**

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FUS Neuromodulation for Refractory Opioid Use Disorder
Randomized Controlled Trial

- 11 participants enrolled – 5 active arm, 6 sham arm (4 crossed over, received active FUS)
  - 10 participants: No device or procedure-related AEs
  - 1 participant (initially randomized to sham) experienced an unexpected adverse device event (UADE) during crossover
    - Pt was found to be unarousable following second sonication
    - MR thermometry showed no temperature increase at the target site
    - MRI revealed microhemorrhages both within and outside the NAc
    - Pt progressively improved over the following weeks and became alert and attentive with intermittent confusion and memory dysfunction
  - Protocol immediately halted on the day of the event

FUS Neuromodulation for Refractory Opioid Use Disorder
Randomized Controlled Trial

- Comprehensive review conducted with our clinical, engineering and neuroradiology teams along with device manufacturer.
  - No underlying differences in the pt relative to the other pts
  - FUS device found to be operating within design and approved specifications
  - Overall pattern suggestive of inertial cavitation with unusual pattern of acoustic signal feedback
- Risk mitigations:
  - Improved sensitivity of device acoustic feedback monitoring & stricter halting criteria
  - Power modulation mode to reduce and adjust power in real-time based on acoustic feedback
  - Increased MRI imaging to improve intra-procedural patient monitoring
- Received FDA approval to proceed with continuation with risk mitigations above
  - 1 participant has received the treatment with no safety concerns

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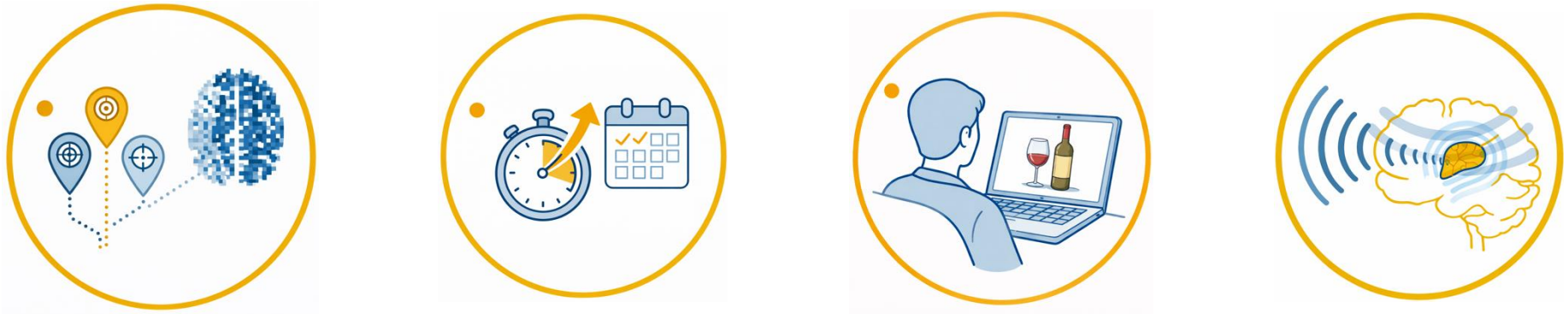
Neuromodulation: Next Steps

- Investigate other devices to improve scalability

- Optimize target location
- Dosing (Length of session, number of sessions, repeated sessions)
- Individualized treatment based on symptom remission (e.g., maintenance session)



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FUS for Psychiatric Disorders: Future Directions

- Other Substances
- Binge Eating Disorder (Currently enrolling – WVU/RNI)
- PTSD (Planned 2026)
- Other Behavioral Addictions (Gambling)
- Depression, Anxiety
- Adolescent Populations

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Addiction Research Program – RNI/WVU Team

Behavioral Medicine
- James Mahoney
- Daisy Thompson-Lake
- James Berry
- Daniel Farmer

Neurosurgery
- Ali Rezai
- Manish Ranjan

Neuroradiology
- Jeffery Carpenter
- Pierre-François D'Haese
- Peng Weng

Research Scientists
- Victor Finomore
- Tasneem Arsiwala
- Geoffrey Adams
- Jacob Suffridge

Clinical & Translational Medicine
- Sally Hodder

Clinical Trial Management
- Padma Tirumalai
- Jennifer Marton

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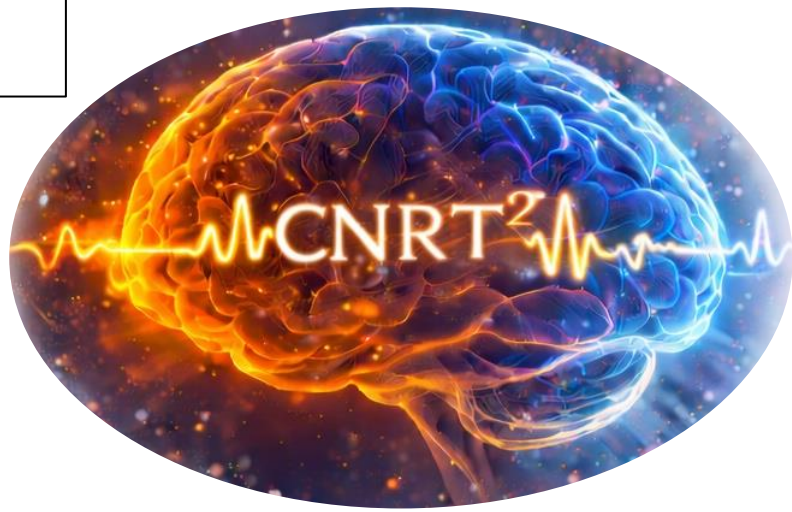
Contact Information:
james.mahoney@uvahealth.org

Center for Neuromodulation Research, Treatment & Technology



Established at the University of Virginia in August 2025 with philanthropic support provided by the Moorman Family.

CPNR Mission:

Investigating ***innovative, cutting-edge*** approaches to complement standard treatments for addiction and psychiatric disorders. With a multidisciplinary focus on research, education, and patient care; improving the lives of those impacted in Virginia and beyond.

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