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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

ABSTRACT

BACKGROUND: Opioid use disorder remains a critical health care challenge because current therapeutic strategies have limitations that result in high recurrence and deaths. We evaluated the safety and feasibility of focused ultrasound (FUS) neuromodulation to reduce substance cravings and use in severe opioid and co-occurring substance use disorders.

METHODS: This prospective, open-label, single-arm study enrolled 8 participants with severe, primary opioid use disorder with co-occurring substance use. Participants received a 20-minute session of low-intensity FUS (220 kHz) neuromodulation targeting the bilateral nucleus accumbens (NAc) with follow-up for 90 days. Outcome measures included safety, tolerability, feasibility, and effects of FUS neuromodulation by assessment of adverse events, substance craving, substance use (self-report, urine toxicology), mood, neurological examinations, and anatomical and functional magnetic resonance imaging (fMRI) at 1, 7, 30, 60, and 90 days post-FUS.

RESULTS: No serious device-related adverse events or imaging abnormalities were observed. Following FUS, participants demonstrated immediate ($p < .002$) and sustained ($p < .0001$; mean 91%) reductions in cue-induced opioid craving, with median ratings on a scale from 0 to 10 as follows: 6.9 (pre-FUS) versus 0.6 (90-day post-FUS). Craving reductions were similar for other illicit substances (e.g., methamphetamine [$p < .002$], cocaine [$p < .02$]). Decreases in opioid and co-occurring substance use were confirmed by urine toxicology. Seven participants remained abstinent at 30 days; 5 participants remained abstinent throughout 90 days post-FUS. Resting-state fMRI demonstrated decreased connectivity from the NAc to reward and cognitive regions post-FUS.

CONCLUSIONS: NAc FUS neuromodulation is safe and a potential adjunctive treatment for reducing drug cravings and use in individuals with severe opioid and co-occurring substance use disorders. Larger, sham-controlled, randomized studies are warranted.

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The addiction crisis in the United States is growing, with increased overdose mortality rates due to the surging prevalence of highly potent synthetic opioids such as fentanyl. The U.S. Centers for Disease Control and Prevention indicated 103,451 overdose deaths in the 12-month period ending in March 2024 (1). Approximately 70% of overdose deaths involve opioids (1), underscoring the ongoing challenge in effectively managing opioid use disorder (OUD). Despite advances in medical treatments, including medication for OUD (MOUD) combined with behavioral and psychosocial interventions, drug-use recurrence (relapse) rates for opioids and other substances remain high, ranging from 50% to 70% following treatment for substance use disorder (SUD) (2,3). Individuals with OUD are increasingly partaking in polysubstance use with drugs that lack medical treatment options, such as methamphetamine (4,5), further contributing to the growing SUD and overdose crisis (6). New treatment modalities are needed given the estimated 1.2 million overdose deaths predicted to occur in the United States and Canada between 2020 and 2029 (7).

Addiction is a chronic medical disorder characterized by neurocircuitry dysfunction (8–10). The nucleus accumbens (NAc) is an integral part of the ventral striatum and plays a key role in the neurobiology of addiction (10,11). The ventral striatum integrates inputs from various brain regions, allowing the modulation of motivational and emotional responses to rewarding stimuli (12). However, chronic exposure to addictive substances may lead to maladaptive changes in

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synaptic plasticity, receptor expression, and signaling pathways of the NAc (13). The role of the NAc in mediating the reinforcing effects of drugs is influenced by its connections to the prefrontal cortex (10) via white matter connections of the internal capsule. Alterations of these connections may explain impaired executive function and inhibitory control observed in individuals with SUD, because this interferes with the ability to regulate behavior and resist drug-related cues (14,15).

Neuromodulation of the reward neurocircuitry using transcranial magnetic stimulation, transcranial direct-current stimulation, and deep brain stimulation (DBS) has been investigated previously (16). DBS allows for precise targeting of deep brain structures such as the NAc and has demonstrated promising results in open-label studies across various SUDs, including OUD (17,18). However, DBS requires invasive surgery with its associated risks and lifelong management of the implantable hardware.

Focused ultrasound (FUS) is a novel, minimally invasive outpatient procedure that can precisely target deep subcortical structures such as the NAc. High-intensity FUS ablative procedures are routinely used worldwide to treat essential tremor and Parkinson's disease (19–21). Neuromodulation is a rapidly emerging application of FUS, which is distinct from lesioning or blood-brain barrier opening. Preclinical studies of FUS neuromodulation have demonstrated safe and reversible inhibition or excitation of subcortical regions without tissue damage (22). In humans, FUS neuromodulation is under investigation for several disorders, including depression, epilepsy, and chronic pain (23).

We previously reported a preliminary safety and FUS dose-finding study of NAc FUS neuromodulation in individuals with primary OUD (24). We now report results of bilateral, simultaneous NAc FUS neuromodulation with a standardized FUS dose in a new cohort of participants with severe primary OUD and co-occurring SUD, describing acute and longer-term effects on opioid and other substance craving and use, emotional symptoms, and exploratory findings on functional brain connectivity.

METHODS AND MATERIALS

Study Design

This prospective, single-arm, open-label trial (Clinicaltrials.gov identifier: NCT04197921) was conducted between February and November 2023 and investigated the effects of low-intensity FUS neuromodulation in participants with severe OUD (6 or more symptoms from the DSM-5 criteria) (25) and co-occurring SUDs. The study was performed at West Virginia University (WVU) Rockefeller Neuroscience Institute and was approved by the WVU Institutional Review Board. An investigational device exemption (IDE #G190092) approval was provided to the device manufacturer (Insightec) by the U.S. Food and Drug Administration. Primary study objectives included assessment of safety, tolerability, and feasibility of bilateral NAc FUS neuromodulation. Secondary objectives included evaluating the acute (1-day post-FUS) and longer-term (7, 30, 60, 90 days) effects on substance use, craving, mood, and functional brain connectivity.

Participants

Participants were between 18 and 60 years of age, with primary OUD, and had been on a stable dose of MOUD (buprenorphine, buprenorphine-naloxone, or methadone) for at least 7 days before the procedure and throughout the post-FUS day 90 follow-up, with the exception of one participant who transitioned from methadone to buprenorphine-naloxone following the day 30 follow-up. A negative urine toxicology screen (excluding cannabis) was required on the day of the FUS procedure. Participants were enrolled in a 28-day residential SUD treatment program at the time of study recruitment. Six participants had the FUS procedure performed while receiving residential treatment (day 24.4 $\pm$ 5.5 of residential). Three participants remained in residential at the post-FUS day 7 follow-up, and all participants were discharged before the post-FUS day 30 follow-up. Following residential treatment discharge, participants were referred to standard of care SUD outpatient treatment (e.g., Intensive Outpatient Program, WVU Comprehensive Opioid Addiction Treatment program). All participants engaged in comprehensive outpatient SUD treatment (group/individual behavioral therapy with MOUD), and 5 participants transitioned to sober living environments. Full inclusion and exclusion criteria are included in the Supplement, section 1.1.

Experimental Procedures

During screening, consented participants completed behavioral (including cue-induced craving assessments), medical (physical, neurological, laboratory, urine toxicology), and magnetic resonance imaging (MRI) assessments. A comprehensive description of screening procedures can be found in the Supplement, section 1.2. Participants received bilateral NAc FUS neuromodulation treatment (described below) with inpatient monitoring for 24 hours post-FUS, at which time behavioral and craving assessments, brain MRI, vital signs, and neurological examination were repeated. The protocol allowed for a second treatment if participants experienced a recurrence of drug use or craving returned to their approximate pre-FUS baseline. Participants returned for in-person follow-up at 7, 30, 60, and 90 days post-FUS, during which safety, behavioral, medical, neurological, imaging, and urine toxicology assessments were performed.

MRI Procedure

Brain scans were performed on a 3T Magnetom Prisma scanner (Siemens). MRI safety sequences included T1 (with and without gadolinium contrast), fast gray matter acquisition T1 inversion recovery (FGAT1R), T2 fluid-attenuated inversion recovery (FLAIR), T2*, diffusion-weighted susceptibility, and gradient echo imaging. Safety scans were performed at baseline; pre- and immediately post-FUS procedure; and at 1, 7, 30, and 90 days post-FUS. Resting-state functional MRI (fMRI) scans were collected at baseline and 7, 30, and 90 days post-FUS. Acquisition details are provided in the Supplement, section 2.1.

FUS Neuromodulation Procedure

The focused ultrasound treatment region targets (the NAc and ventral anterior internal capsule) were identified using T1,

FGAT1R, and susceptibility weighted imaging MRI sequences, as previously performed in our DBS and FUS studies (17,24,26). The center of this target corresponds to ranges of 7 to 11 mm from the midline, 2 to 5 mm anterior, and 0 to 3 mm below the anterior commissure. The treatment region is further refined by identifying streamlines generated from diffusion-weighted imaging. Our targeting approach carefully balances the inclusion of the NAc and white matter tracts within this defined region, optimizing the overlap to engage key neural pathways, for example, the medial forebrain bundle, anterior thalamic radiation, and corticostriatal connections. This targeted approach ensures precise modulation of relevant circuits. Participants underwent either head shave or hair trimming (<1 inch). The first 4 participants underwent FUS neuromodulation with the frameless dental mold assembly (DMA) while the others had standard stereotactic frame. Our MRI-guided, FUS protocol employed the ExAblate Neuro Type 2 (Insightec) device with a 220-kHz hemispheric transducer helmet comprising 1024 ultrasound transducers that converge to our defined target focal point (24). As soon as the participants were in the MRI scanner, they received behavioral and craving assessments followed by an initial 5-minute (300 seconds) session during which no energy was delivered (zero-energy FUS), and craving assessments were repeated (to serve as comparison to the subsequent active FUS sessions). Next, 4× 5-minute (300 seconds) block sessions of active FUS (8 subspots, 90–100 W therapeutic energy; duty cycle = 3.3% per subspot; 100 repetitions; TR = 3 seconds; pulse duration = 100 ms) were delivered to the bilateral NAc (up to a total of 20 minutes of active FUS). All block sessions were single-blinded (participant only).

Cue-Induced Craving Procedure

Throughout the FUS neuromodulation procedure, participants were exposed to substance-related cues (images of illicit substances and drug-related paraphernalia) via MRI-compatible goggles. Rating scale responses were collected via button boxes where participants moved a cursor from "no craving" (0 on rating scale) to "most craving ever" (10 on rating scale) (24), and responses were extracted for analysis. The substance-related stimuli and craving questions were individualized for each participant based on their 3 most used substances and route of administration (e.g., oral, smoking, nasal, or intravenous). Images were taken from a database of over 800 drug images to reduce risk of repetition and habituation. Questions regarding mood (depression and anxiety) were asked in a similar fashion. During screening and follow-up visits, participants completed a cue-induced craving task (cue reactivity) (27) on a laptop computer and provided their craving and mood ratings. Although stimuli were personalized to the participant's substances of choice, participants were asked to provide their rating for all substances (heroin, opioids, fentanyl, methamphetamine, cocaine, benzodiazepines, cannabis, alcohol, and nicotine).

Outcome Measures

The primary end points were safety, tolerability, and feasibility throughout the 90-day follow-up period. Adverse events (AEs) were assessed prior to, during, and following FUS via self-report and clinical evaluations. Participants were asked about headache, general systemic symptoms, and neurological and behavioral changes during standard clinical encounters. Behavioral assessments included the Hamilton Depression Rating Scale (HDRS) (28) and the Columbia Suicide Severity Rating Scale (CSSRS) (29). Evaluations of anhedonia and pleasure (the Snaith-Hamilton Pleasure Scale) (30) and positive affect, satisfaction, and energy (Neuro-Quality of Life subscales: Positive Affect and Well-Being, Satisfaction with Social Roles and Activities, and Fatigue) (31) were administered to assess for reductions in pleasure or enjoyment in non–substance-related activities (data acquired from participant numbers 5–8 after protocol amendment). Brain MRIs were performed immediately after FUS treatment and at 1, 7, 30, and 90 days post-FUS to assess for imaging abnormalities. Secondary outcome measures included substance use assessed via urine toxicology (gas chromatography–mass spectrometry) and self-report; cue-induced substance craving; and mood at 1, 7, 30, 60, and 90 days post-FUS. Resting-state fMRI was assessed at baseline and 7, 30, and 90 days post-FUS. Study timeline and end point assessments can be found in Table S1.

Statistical Analyses

Safety, Substance Use, and Substance Craving Analyses. For safety, frequency and descriptive analyses were performed for AEs assessed throughout the 90-day post-FUS follow-up period. For substance use, frequency and descriptive analyses were performed for substance use (urine toxicology). For craving and mood, because participants reported different preferences for fentanyl, opioids, and heroin, the median craving rating of these 3 opioid scores was used for analysis. Given the modest sample size, Bayesian data analysis was used, facilitating evaluation and interpretation of the clinical impact of FUS (32). We calculated posterior probabilities and present our findings using the Bayes factor (BF) representing strength of evidence (33). For short-term changes in opioid craving after cue presentation (from baseline to 1 day post-FUS), we used paired t tests. Longer-term changes in cravings and emotional symptoms (anxiety and depression) were analyzed using repeated-measures analysis of variance (ANOVA) at multiple time points (baseline, 7, 30, 60, and 90 days post-FUS). Bayesian analyses were conducted in JASP (version 0.18.3). Traditional statistical significance levels are also reported; analyses were conducted with SPSS (version 29.0; IBM Corp.). Analysis and results of within-session opioid craving during active and nonactive FUS can be found in the Supplement, section 2.2.

Resting-State fMRI Data Analyses. fMRI data were preprocessed using SPM12 (34) and denoised and analyzed with CONN version 22a functional connectivity toolbox (35). We projected the data onto the Montreal Neurological Institute (MNI) space. The left and right NAc were selected as seeds from the CerebrA atlas (36). Connectivity analyses between the NAc and the whole brain were conducted at each time point (baseline and 7, 30, and 90 days post-FUS) using a cluster-forming ($p < .005$) voxel-level threshold and a false discovery rate (FDR) ($p_{FDR} < .05$) cluster-size threshold. We conducted 2

analyses: 1) whole-brain functional connectivity with NAc at each individual time point and 2) significant changes from baseline (contrast analysis: 7 days vs. baseline; 30 days vs. baseline; 90 days vs. baseline). The detailed methods can be found in the Supplement, section 2.3.

RESULTS

Participant Characteristics

A total of 8 participants (6 men, 2 women; median age 35.5 [range 23–48 years]) constituted the study population for this report (see CONSORT [Consolidated Standards of Reporting Trials] diagram in Figure 1). Participants met DSM-5 criteria (25) for severe OUD and reported excessive non-opioid substance use. Participants reported a median 14.1-year (range 4–36 years) history of heroin or fentanyl use and a median 14.9-year (range 1–37 years) history of prescription opioid use. Years and frequency of co-occurring, non-opioid substance use can be found in Table 1 (characteristics for each participant are presented individually in Table S2). Two participants met criteria for substance-induced anxiety, and 4 participants met criteria for substance-induced depression given the onset of their symptoms coinciding with the onset of their substance use. Seven of the 8 participants had unsuccessful past treatment attempts (median 4; range 3–10+ attempts) across outpatient, inpatient, detoxification, and residential treatment settings, and 6 participants had at least 1 past drug overdose, 5 of whom reported multiple past overdoses (median 4; range 1–5+).

Safety and Tolerability of FUS Neuromodulation Procedures

No safety concerns were presented during the FUS procedures or days 1, 7, 30, 60, or 90 follow-up evaluations. All participants were scheduled to complete four 5-minute block sessions for a total of 20 minutes of active FUS. However, 1 participant opted to end the procedure early due to discomfort from the DMA. There were no unexpected AEs and no serious AEs related to the FUS procedure. There was one serious AE (drug overdose) deemed not to be related to the procedure. There were 9 mild AEs (most commonly headache) and 1 moderate AE (anxiety) that were procedure related (refer to Table S3 for detailed AEs). Behavioral examinations (HDRS, CSSRS) at all assessments were normal with no evidence of clinically meaningful increases in depression (Table S4) or suicidality immediately after the procedure or at any of the follow-up time points. There was no strong suggestion of increased anhedonia or reduction in pleasure or satisfaction such as food enjoyment (Table S5). Brain MRI acquired immediately following FUS and on days 1, 7, 30, and 90 post-FUS follow-up were evaluated by a neuroradiologist (JC) and neurosurgeons (AR, MR) and did not demonstrate edema, hemorrhage, or any notable changes in brain structure. Participants self-reported being unable to correctly identify the active FUS sonication treatment from blocks where no FUS sonication was given based on any physical experiences during the procedure.

Cue-Induced Substance Craving and Mood

Acute Changes. There was decisive evidence (postactive vs. pre-nonactive FUS [BF_{10} = 178.4]) and moderate evidence (postactive vs. post-nonactive FUS [BF_{10} = 6.6]; postactive vs. preactive FUS [BF_{10} = 6.7]) supporting a difference between postactive FUS and preactive FUS conditions indicating that craving was changed after active FUS treatment (Figure S1). A Bayesian 2-sided paired *t* test (Cauchy's prior = 0.707) revealed strong evidence for reduction in opioid craving from baseline to day 1 post-FUS (BF_{10} = 28.1), where BF_{10} gives

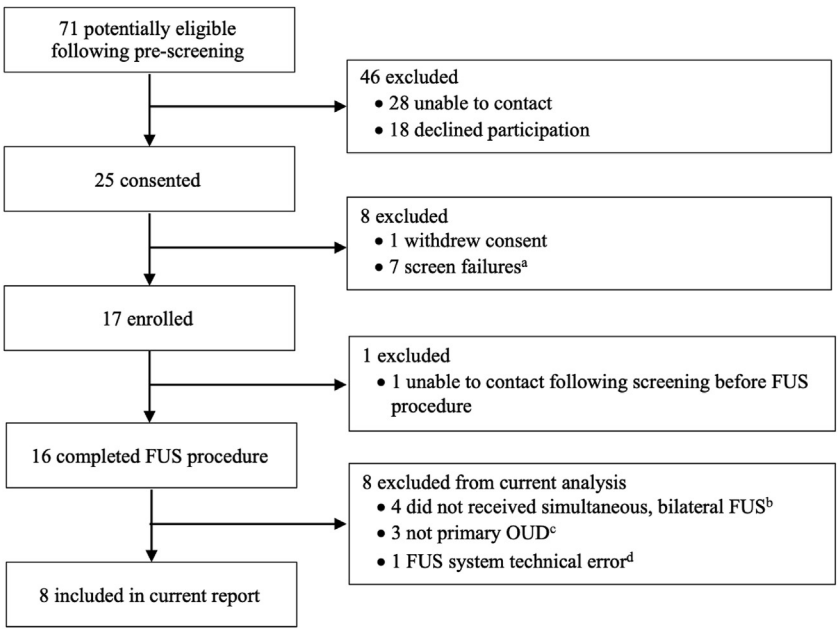

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. Of the 8 participants who were included in the final analyses, the individual data for 1 participant have been published previously as a case report (26). [a]Screen failures (*n* = 7): from claustrophobia (*n* = 4), abnormal labs (*n* = 1), inability to be contacted to complete screening (*n* = 2). [b]Enrolled in initial safety, dose-escalation protocol, where focused ultrasound (FUS) was applied to the nucleus accumbens unilaterally and sequentially (*n* = 4) (24). [c]Participants with a diagnosis other than primary opioid use disorder (OUD). [d]FUS device malfunction (software and technical issues) preventing appropriate dose delivery and completion of procedure (*n* = 1).

Table 1. Participant Demographic and Substance Use Characteristics

	Median [Range] or *n*
Participant Characteristics	
Age, Years	35.5 [23–48]
Sex, Female/Male	2/6
Past Overdoses[a]	4 [1–5+]
Past Substance Use Disorder Treatment Attempts[a]	4 [3–10+]
Opioid Use Characteristics	
Specific Opioids Used: Heroin or Fentanyl	
Years of use	14.1 [4–36]
Primary route of use	3 intravenous, 5 smoking
Specific Opioids Used: Prescription Opioids	
Years of use	14.9 [1–37]
Primary route of use	1 intravenous, 2 smoking, 4 nasal, 1 oral
Non-Opioid Substance Use, Years of Use[b]	
Methamphetamine, *n* = 8	9.0 [1–26]
Cocaine, *n* = 6	19.0 [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]

[a]Seven of the 8 participants had unsuccessful past treatment attempts across outpatient, inpatient, detoxification, and residential treatment settings, and 6 participants had at least 1 past overdose, 5 of whom reported multiple past overdoses.

[b]*n* represents the number of participants who were diagnosed with a co-occurring substance use disorder and/or who reported co-occurring non-opioid substance use.

evidence for the alternative hypothesis. The results of a 1-sided *t* test provided very strong evidence that craving was reduced acutely post-FUS (BF_{10} = 56.1; median effect size of 1.5; 95% CI, 0.4–2.7).

Longer-Term Changes. Evaluating changes in opioid craving over extended time points (7, 30, 60, and 90 days) from baseline (repeated-measures ANOVA) revealed decisive evidence that changes in opioid craving occurred over time (BF_{10} = 1048.3) (Figure 2). Cravings for other substances decreased from baseline to all follow-up visits (Figure 3). Bayesian repeated-measures ANOVA for the same time points indicated moderate evidence for reduced depression over time (BF_{10} = 4.2) and weak evidence for reduction in anxiety (BF_{10} = 2.9) (Figure S2).

Following FUS neuromodulation, participants demonstrated immediate and sustained reduction (mean 91%) in cue-induced opioid craving (scale from 0 to 10 where 10 = most craving: 6.9 pre-FUS vs. 0.6 at day 90 post-FUS). Descriptive statistics are summarized in Table S6. Individual opioid and other substance craving ratings for each participant across the time course can be found in Figure S3.

Substance Use During Follow-Up Visits

Urine toxicology results (Table 2) revealed that all participants were negative for all assessed substances on 1 and 7 days post-FUS. During the 30-day follow-up, 7 participants were entirely abstinent; during the 60- and 90-day follow-up assessments, 5 participants were entirely abstinent. One participant had a second FUS treatment following a relapse after the 60-day follow-up and therefore did not complete the 90-day follow-up. Self-reported substance use provided by participants at each follow-up visit were consistent with urine toxicology results and represented a substantial reduction from their estimated pre-FUS, baseline substance use patterns/frequency (Table S7).

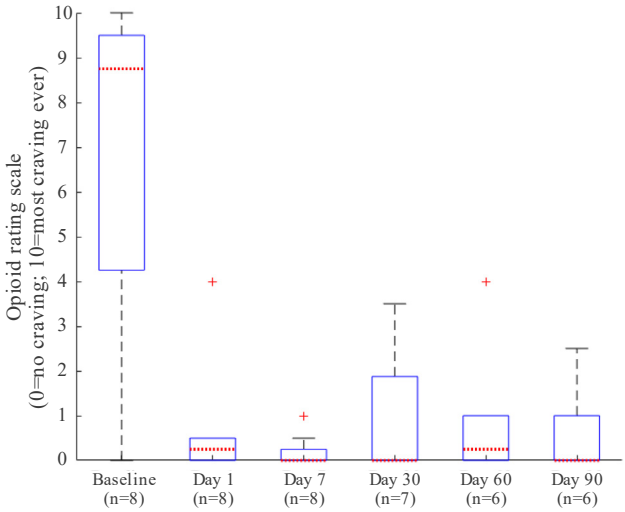

Figure 2. Opioid craving after cue exposure during baseline (before focused ultrasound [FUS]), acutely post-FUS (follow-up day 1), and longer-term (days 7, 30, 60, 90 follow-up). One participant did not complete cue-induced craving during day 30, 60, or 90 follow-ups due to clinical concerns (risk of drug use recurrence). One participant missed the day 60 follow-up due to unrelated illness. One participant who relapsed was retreated (per protocol) with FUS prior to the day 90 follow-up; the data were not included at the day 90 follow-up. The blue boxes show interquartile range (middle 50% of scores); the red dotted line within boxes shows the median (if applicable); the black dotted line shows the range of reported scores; + indicates outlier.

Functional Connectivity Analyses

Functional connectivity analyses were conducted only on data from participants who remained abstinent (day 7 [*n* = 8], day 30 [*n* = 7], and day 90 [*n* = 5]). Analysis of each time point individually, with the NAc as a seed region, demonstrated clusters with a marked decrease in positive connectivity from the NAc to the ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC), and posterior cingulate cortex (PCC) ($p_{FDR} < .05$) (Figure 4). Notably, the bilateral ACC cluster reduced from 20,640 mm^3 (baseline) to 17,469 mm^3 (7 days) to 2015 mm^3 (30 days) and to 859 mm^3 (90 days) with similar declines in the vmPFC and PCC (Table S8). Consistent positive connectivity between the NAc and ventral striatum was demonstrated, as well as unchanged negative connectivity with temporo-occipital regions ($p_{FDR} < .05$) (Figure S4).

The second functional connectivity analysis comparing follow-up time points to baseline revealed several regions with significant reduction in connectivity strength from baseline

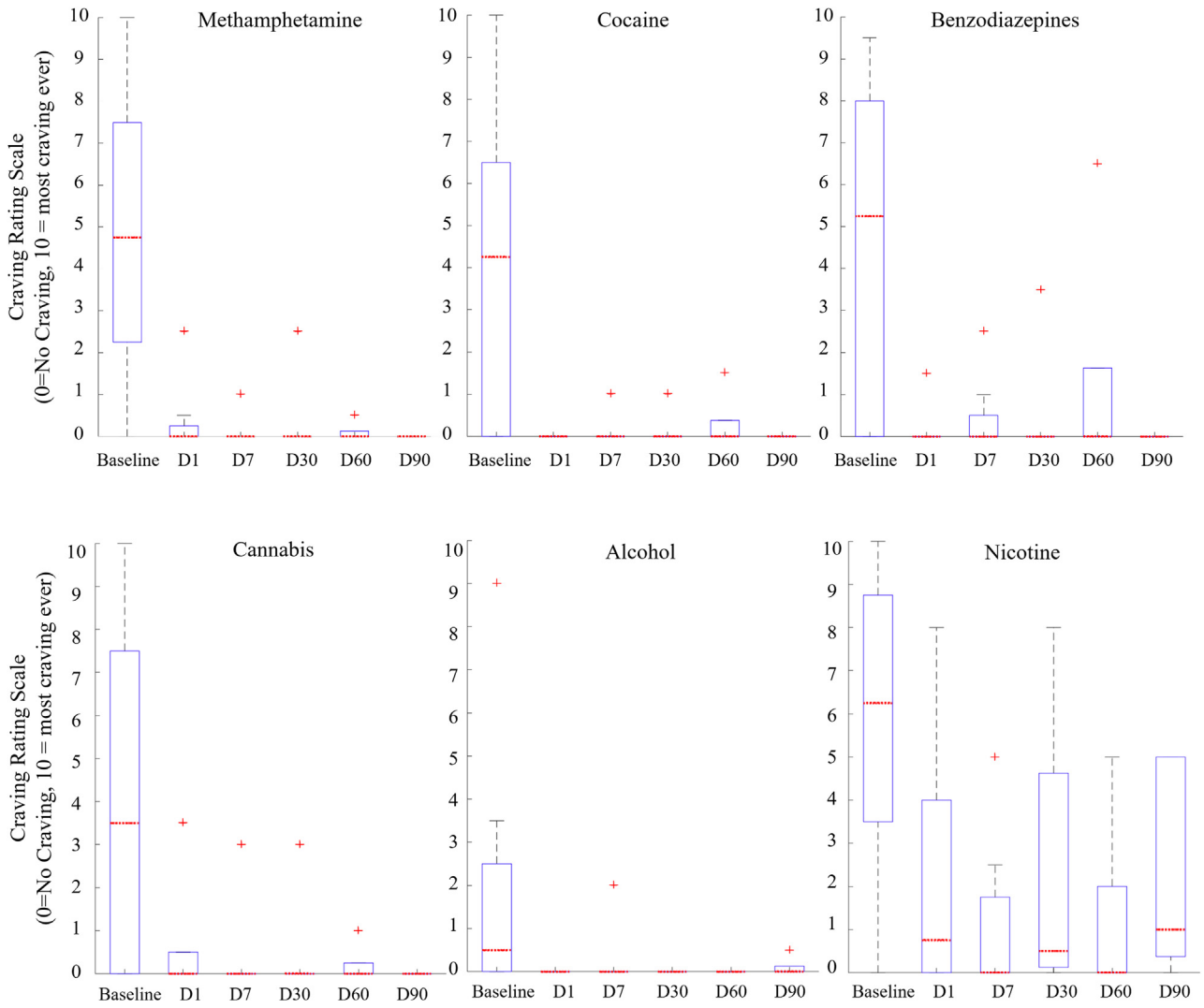

Figure 3. Non-opioid craving after cue exposure at baseline (before focused ultrasound [FUS]) and post-FUS (day 1, 7, 30, 60, 90 follow-up). The resulting samples at each cue reactivity time point were as follows: baseline, day 1, and day 7 (n = 8); day 30 (n = 7); day 60 (n = 6); and day 90 (n = 6). The blue boxes show interquartile range (middle 50% of scores); the red dotted line within boxes shows the median (if applicable); the black dotted line shows the range of reported scores; + indicates outlier.

(Table S9). Reductions were found between the NAc and several regions, including the dorsolateral PFC (dlPFC), PCC, and PFC ($p_{FDR} < .05$) (Figure S5); sparse clusters of increased connectivity are also reported.

DISCUSSION

Our study demonstrates that bilateral FUS NAc neuromodulation is a novel, safe, well-tolerated, and feasible treatment modality for severe OUD and co-occurring SUDs. Relative to pre-FUS baseline, there was a substantial reduction in substance craving (mean 91%) across all participants. Five participants were abstinent from all substances, which was verified via urine toxicology, throughout the 90-day follow-up period. In the 3 participants with recurrence, drug use was less frequent compared with pre-FUS use and occurred in the absence of craving. Specifically, participants noted that pre-FUS, craving preceded drug use recurrence; however, post-FUS drug use was not associated with craving (e.g., recurrence occurred to avoid withdrawal after not being able to obtain their MOUD or due to psychosocial factors such as habitual use with a partner). Furthermore, unlike pre-FUS, when recurrence was associated with continued substance use for several weeks or months before reinitiating treatment, study participants rapidly reengaged with treatment. These results contrast with patients on existing treatments and are noteworthy because the findings occurred in the context of a single FUS neuromodulation treatment.

Table 2. Quantitative Urine Toxicology During Baseline and Follow-Up Assessments

Participant	Pre-FUS, Baseline[a]	Post-FUS Day				
		1	7	30	60	90
1	–	–	–	–	–	–
2	–	–	–	–	–	–
3	–	–	–	+ (fentanyl, opiates, cannabis)	–	–
4	–	–	–	–	+ (fentanyl, cannabis)	+ (cannabis)
5	–	–	–	–	–	–
6[b]	–	–	–	–	+ (fentanyl)	NA
7	–	–	–	–	–	–
8	–	–	–	–	–	–

"+" indicates that the participant tested positive for the noted substances: fentanyl, cannabis, opiates, or NA. "−" indicates that the participant tested negative for all substances.

FUS, focused ultrasound; NA, not available.

[a]Participants were recruited from a residential treatment program, and therefore urine toxicology was not reflective of their typical use.

[b]Following the day 60 follow-up, participant received a second FUS treatment per protocol following drug use recurrence.

There were no FUS-related neurological or behavioral AEs and no impact on other pleasurable activities. Our key finding of immediate and sustained reduction in cravings and reduction of use of opioids and other substances following just one FUS neuromodulation treatment highlights the potential of this intervention. This response was surprising considering the severity of SUDs among study participants. Although the NAc is implicated in emotional regulation, we saw no unwanted side effects (e.g., anhedonia) in the cohort. In fact, all participants showed an improvement in depression, anxiety, and behavioral and psychosocial functioning as observed by participants, care providers, and family. We believe that improvements in mood coupled with decreased cravings contributed to the reduction in substance use. An example that supports this is participant number 6, who experienced a recurrence of drug use and subsequent overdose. Although his craving increased measured at day 30 and day 60 post-FUS follow-ups compared with earlier visits (yet remained lower than his pre-FUS baseline), there was evidence of increased depression, anxiety, and fatigue, together with decreased positive affect and satisfaction with social roles over time.

The mechanism of FUS neuromodulation is a focus of preclinical and functional brain imaging investigations. Preclinical studies have shown that FUS energy can mechanically alter cellular membranes, impacting transmembrane currents and mechanosensitive ion channel activation and potentially altering signal transduction activity and changes in gene expression (20,37,38). Our resting-state fMRI findings suggest that post-FUS reductions in drug craving and substance use are accompanied by decreases in functional connectivity in the brain's reward circuitry (NAc, ACC, vmPFC) and cognitive control systems (dlPFC). Our baseline findings (prior to FUS) results were comparable to those of a recent meta-analysis of resting state in SUD populations that found hyperconnectivity in reward networks such as the ventral striatum (NAc) and medial frontal cortex (ACC, vmPFC) (39). After FUS, we noted connectivity reductions in cluster size in cortical regions (ACC, vmPFC, PCC, and dlPFC) and in connectivity strength to the PCC and dlPFC. The observed decreases in connectivity strength between the NAc and the dlPFC suggest that FUS may modulate the relationship between the reward network and executive functioning such as decision making.

Strengths and Limitations

Our findings should be interpreted in the context of the following limitations. While evidence of reduction in substance craving and use was clearly observed, the open-label design and modest sample size precludes drawing definitive conclusions. A limitation is that we are unable to account for potential

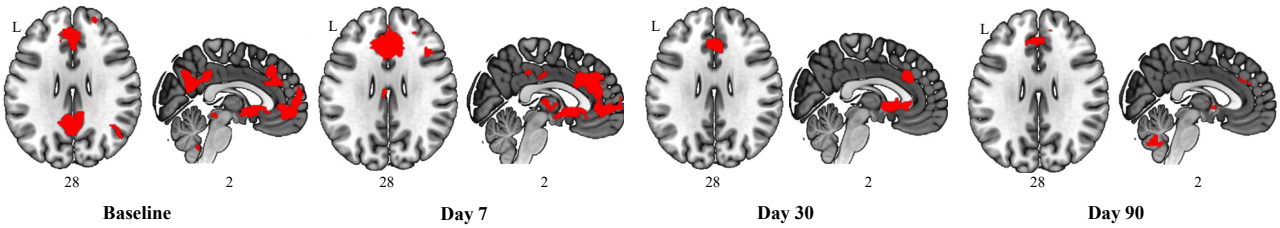

Figure 4. Functional connectivity of the nucleus accumbens (NAc). Results used a seed-to-whole brain analysis, applying a cluster-forming voxel-level threshold ($p < .005$) and a cluster-size threshold (false discovery rate–corrected $p < .05$) to identify voxels significantly connected with the NAc. Connectivity of NAc to whole brain at individual time points shows decreases in positive connectivity cluster size from baseline to post-focused ultrasound time points for the anterior and posterior cingulate cortices and the ventromedial prefrontal cortex. L, left.

placebo effects. Our randomized, sham-controlled clinical trial with a larger number of participants and longer follow-up is in the early stages of enrollment. The data acquired from the sham arm will provide meaningful data to control for residential inpatient treatment and potential placebo effects. Although we cannot isolate the effects of residential treatment from those related to the FUS procedure, participants reported high cravings prior to FUS, regardless of their time in treatment or sober living. Another limitation is the generalizability of individuals who are not taking MOUD. Given the novelty of FUS neuromodulation, the intention of this open-label investigation was to study the impact of FUS as an adjunctive treatment to the current standard of care (which includes MOUD and behavioral treatment). Future studies should investigate FUS neuromodulation in the absence of MOUD and determine whether craving remains reduced after MOUD has been tapered. In addition, while this cohort received FUS after completing detoxification and being stabilized in residential treatment, future studies conducted while participants are experiencing acute withdrawal may provide insight into the use of FUS in reducing symptoms during the initial phases of treatment (e.g., detoxification). Acquiring biological measures of cue exposure (e.g., heart rate, blood pressure, skin conductance) to complement self-report measures during cue exposure may provide further insight. While participants self-reporting the context surrounding drug use recurrence (i.e., not due to craving but due to other factors) provides useful anecdotal evidence, collecting this information objectively and methodically will be critical to further elucidating contributory factors to drug use recurrence.

Given the findings of reduced craving for non-opioid substances without available medical treatments (e.g., methamphetamine), the positive impact of FUS neuromodulation in reducing opioid craving in the absence of MOUD is certainly plausible. The duration of effect is unknown, as is the number of FUS treatment sessions required for long-lasting changes in drug-taking behavior. The day 90 craving data for the participant who underwent a second FUS treatment shortly after day 60 were excluded from the final analysis. Following this second treatment, his craving ratings decreased to 0 for all substances except benzodiazepines (0.5 out of 10), indicating potential additive effects of repeated FUS treatments that warrant further investigation. Despite these limitations, the current findings are promising and demonstrate the need for further investigation of FUS neuromodulation as a potential adjunctive treatment for OUD and other SUDs.

Conclusions

Our results show that in drug abstinent participants, bilateral NAc FUS neuromodulation for severe, primary OUD and co-occurring SUD is safe and associated with reduced substance craving and use. The FUS neuromodulation procedure has the inherent advantages of being an outpatient procedure that can precisely target and modulate deep brain structures implicated in addiction. While this study focused on severe, primary OUD, our observation of the impact of FUS neuromodulation on reducing cravings and use of methamphetamine, cocaine, and other substances holds promise for treatment of SUDs other than OUD, especially those with no current medication treatments.

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All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AR, MR, VF, and JJM were responsible for concept and design. DGYT-L, P-FD, NM, MR, DF, JLM, JC, AB, and JJM were responsible for acquisition, analysis, or interpretation of data. AR, DGYT-L, P-FD, MR, VF, SH, and JJM were responsible for drafting of the manuscript. AR, DGYT-L, P-FD, MR, JB, SH, OB, GA, and TAA were responsible for critical review of the manuscript for important intellectual content. DGYT-L, P-FD, NM, and JJM were responsible for statistical analysis. AR and VF were responsible for obtaining funding. VF, JLM, and PT were responsible for providing administrative, technical, or material support. AR, VF, OB, and JJM were responsible for supervision.

The data generated and analyzed during this study are available upon reasonable request and justification. Researchers who are interested in accessing the data should submit their inquiries and rationale for data access to the following email address: ptirumalai@hsc.wvu.edu. Each request will be evaluated to ensure compliance with participant confidentiality and ethical research standards.

The authors report no biomedical financial interests or potential conflicts of interest.

ClinicalTrials.gov: A Feasibility Clinical Trial of Exablate for Low Intensity Focused Ultrasound Neuromodulation in Patients with Opioid Use Disorder (OUD) And/or Other Substance Abuse Disorders (SUDs); https://clinicaltrials.gov/study/NCT04197921; NCT04197921.

ARTICLE INFORMATION

From the Department of Neurosurgery, Rockefeller Neuroscience Institute, West Virginia University, Morgantown, West Virginia (AR, MR, AB); Department of Neuroscience, Rockefeller Neuroscience Institute, West Virginia University, Morgantown, West Virginia (DGYT-L, DF, VF, JLM, JB, PT, GA, TAA, JJM); Department of Neuroradiology, Rockefeller Neuroscience Institute, West Virginia University, Morgantown, West Virginia (P-FD, JC); Laboratory of Cognitive Neuroscience, Neuro-X Institute, Swiss Federal Institute of Technology, Geneva, Switzerland (NM, OB); Department of Behavioral Medicine and Psychiatry, Rockefeller Neuroscience Institute, West Virginia University, Morgantown, West Virginia (DF, JB, JJM); and West Virginia Clinical & Translational Science Institute, West Virginia University, Morgantown, West Virginia (SH).

Address correspondence to James J. Mahoney III, Ph.D., at james.mahoney@hsc.wvu.edu.

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