Title: Personalized cue-reactive delta-theta oscillations guide deep brain stimulation for opioid use disorder

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Abstract / Summary

Substance use disorders (SUDs) are a significant public health concern, with over 30% failing available treatment. Severe SUD is characterized by drug-cue reactivity that predicts treatment-failure. We leveraged this pathophysiological feature to personalize deep brain stimulation (DBS) of the nucleus accumbens region (NAc) in an SUD patient. While this DBS lead was externalized for clinical purposes, we administered a personalized drug cue-reactivity task while recording NAc electrophysiology. We identified a cue-evoked signal in the ventral NAc associated with intensification of opioid-related cravings, which attenuated with therapeutic stimulation delivered to this same area. DBS was then programmed to engage this subregion within NAc to account for the biomarker location, heralding the potential for personalized strategies to optimize DBS for SUD.

Keywords:

Cue reactivity; Deep brain stimulation; Electrophysiological biomarker; Opioid use disorder

Declaration of Interests

C.H.H. has patents related to sensing and brain stimulation for the treatment of neuro-psychiatric disorders (USPTO serial number: 63/170,404 and 63/220,432; international publication number: WO 2022/212891 A1) as well as use of tractography for circuit-based brain stimulation (USPTO serial number: 63/210,472; international publication number: WO 2022/266000). C.H.H. is a consultant for Boston Scientific, Abbott, Medtronic, and Insightec and receives honoraria for educational lectures. The other authors declare no competing interests.

Acknowledgments

C.H.H is supported by the National Institute of Health (5UH3NS103446-02 and U01NS117838) and the Foundation for OCD Research. The authors would like to thank the study subject for his participation and commitment to this novel, exploratory application.

Substance use disorders (SUDs) are a growing public health concern of epidemic proportion, resulting in more than 100,000 annual deaths in the United States alone[1]. The biggest challenge to treatment success in SUD is preventing relapse, the risk of which has been attributed to neural adaptations in the frontostriatal circuitry involving the nucleus accumbens, an important component of the mesolimbic dopamine system[2–5]. Deep brain stimulation (DBS) is a long-term neuromodulatory treatment with the potential to rescue these adaptations and reverse behavioral sensitization to drug in severe cases[6]. However, the best way to engage the accumbens network with DBS in SUD remains largely unknown in humans[7].

Functional neuroimaging assays have utilized cue-reactivity paradigms in SUD to probe neural activity underlying compulsive drug seeking and drug ingestion[4,8,9]. Hyperreactive responses due to sensitization to drug-related cues have been associated with poorer treatment outcomes and increased relapse rates[10–12]. However, a well-recognized challenge with functional MRI is its limited spatial and temporal resolution. In this rare case study, we seized a serendipitous opportunity to synchronize a cue-reactive paradigm to intracranial electroencephalographic (iEEG) recordings via an *in-situ* nucleus accumbens (NAc) DBS electrode that afforded high spatial and temporal resolution to decipher the involvement of the NAc region in drug-related cravings and behavior[8,13]. We report the identification and use of a cue-reactive electrophysiological biomarker to optimize DBS programming in a patient with opioid use disorder (OUD), heralding the potential for personalizing DBS using an objective read-out of at-risk pathophysiology.

The subject is a 26-year old male with existing bilateral globus pallidus interna DBS implanted for the treatment of tardive dystonia and left NAc DBS to treat his severe OUD[14] (off-label treatment, see online Methods; Fig S1a). The DBS treatment improved his OUD and substance cravings, allowing him to abstain from drug use for several years. However, a very high dose of stimulation (14.5mA) in the ventral anterior limb of the internal capsule (vALIC) (DBS contacts 4-5) was required to achieve this, which led to rapid charge depletion of the IPG. His intravenous opioid drug use was also complicated by infective endocarditis requiring multiple cardiac surgeries. A subsequent wound erosion over the left subclavicular incision warranted removal of the DBS IPG, which was followed by a rapid recurrence of his opioid cravings and drug-related thoughts (Fig 1a). He then presented to our institution for further management.

Due to clinical suspicion for ongoing wound infection, his DBS system was externalized with an extension cable while cultures and antibiotic treatment ensued. During this period, personalized computer-based cue-reactivity tasks were performed to identify and localize a potential electrophysiological biomarker of drug cue-reactivity by recording brain activity from the DBS lead. We hypothesized that prior charge density requirements were due to non-specific engagement of the NAc region from the ventral limb of the internal capsule stimulation site. With the goal to identify where cue-reactivity was most robust and specific to relevant drug cues, we conducted three computer-based tasks: a primary drug cue-reactivity task to assess for presence of drug-related biomarker[10] (Fig 1b), the Monetary-Incentive-Delay, MID[15] and the Urge-for-Action Task, UFAT[16] (online methods, Fig S2 and S3). The two latter tasks were used as behavioral controls to assess specificity of electrophysiologic drug-cue reactivity.

Time-frequency analysis of the data demonstrated that upon presentation of personalized drug-related cues, a robust elevation of a low-frequency band (1-7Hz) power in the local field potential was identified in the ventromedial-most region of the NAc, the presumed shell

subregion[17,18] (contacts 1-2) (Fig 1c). This task-induced cue-reactivity correlated with the patient's ratings of drug cravings on a visual analog scale (VAS; range 1-9). This potential low-frequency biomarker was not present in any other electrode contact pair along the DBS lead (Fig 1d & S1b), suggesting anatomical specificity, which is not surprising given the NAc subregions are distinguished both anatomically and functionally[19]. Moreover, the electrographic features of this biomarker were not elicited with non-drug incentive cues using the tasks intended for behavioral control (Fig S2a-b and Fig S3).

Next, a systematic stimulation assessment was conducted across the DBS electrode contact pairs per usual clinical practice to identify the optimal stimulation targets with the widest therapeutic window. A summary of the assessment is shown in Fig 2a. This aligned with selection of the NAc shell as the optimal stimulation site, with reduction of cravings noted at the lowest dose required (5-6mA, 90µs, 130Hz) without adverse effects. Positive effects were noted at more dorsal contacts in the vALIC (contacts 4+/5-) where he was previously stimulated, although higher stimulation doses (8mA) were required during the evaluation. Sham-controlled stimulation was then performed to confirm the acute effects of stimulation observed were not placebo effects.

We then investigated the effect of acute stimulation to the NAc shell (contacts 1-2) on iEEG recordings during the drug cue-reactivity task and found that stimulation attenuated the craving-related increase in low frequency power, which correlated with a reduction in clinical ratings of craving (Fig 1e-f). As stimulation artifact precludes monitoring iEEG signals simultaneous with stimulation, DBS pretreatment was delivered for ten minutes (1-/2+, 6mA, 90µs, 130Hz) prior to administration of the task, and an additional 15s stimulation period was delivered before each cue presentation (Fig 1b). This interdigitated approach allowed for the observation of stimulation effects without introducing artifact. With DBS stimulation on, upon presentation of the drug cue videos, average power of the 1-7 Hz low-frequency signal was significantly reduced as compared to without stimulation (*$p<0.05$, Student's t-test). This reduction in low-frequency band power correlated with >50% reduction in mean subjective rating of opioid-related cravings by the subject (6.93 vs 3.09, *$p<0.001$, Student's t-test) (Fig 1f).

Based on these clinical and electrophysiological findings, chronic DBS parameters were selected (1-/2+, 6mA, 90µs, 130Hz) that required less than half of the original stimulation dose (14.5mA). Six months following this DBS personalization, the subject reported sustained reduction in drug cravings and continued abstinence from opioid use, meeting DSM-V criteria for early remission (Fig 2b). He also reported improvement in inhibitory thoughts and ability to resist unwanted cravings for substances. Connectivity analysis of the two stimulation sites revealed that the original stimulation setting had a much larger (25x) volume of tissue activation (VTA) (896mm^3 vs 35.4mm^3), overlapping with the NAc shell region, with non-specific activation of other brain regions (Fig 2c-h). This suggests that our personalized strategy was useful to guide a more precise stimulation delivery with similar therapeutic efficacy while balancing device charge drainage.

In this case study, we leveraged a unique clinical opportunity that demanded a need to understand the electrophysiological underpinnings of opioid cravings to optimize DBS therapy. Personalized cue-reactive low frequency oscillatory activity localized to the presumed human NAc shell guided a sustainable DBS intervention. This novel proof-of concept establishes a foundation for developing personalized DBS approaches for SUD. To our knowledge, there is

only one other report of iEEG in individuals with OUD, where prominent resting state theta- and alpha-frequency activity of the ALIC and NAc were recorded[20]. Our novel paradigm of pairing a personalized cue-reactivity task with iEEG recording enabled identification of an electrophysiological response that redirected DBS programming away from the vALIC to the NAc shell region. Similar electrophysiological approaches have been used to successfully identify biomarkers of compulsion in subjects with obsessive-compulsive disorder and loss of control eating[21–24]. Based on results of personalized tractographic structural connectivity analysis, it is postulated that the positive effects on opioid cravings from the original DBS stimulation parameters were due to effects in the NAc, which is well-known to be involved in neural adaptations underlying drug-related behavioral sensitization[5]. While electrophysiological target localization is increasingly investigated to optimize DBS for clinical applications and investigational studies[25–27], this is the first demonstrated use for target engagement in a subject with SUD to optimize DBS therapy. A basic modelling of charge requirement with this new stimulation paradigm predicted substantially improved battery lifespan (Energy Use Index 12.3 vs 39.3) of the subject's pulse generator, further emphasizing the need for precision targeting and personalization of DBS therapy.

The presence of a drug-cue reactive electrophysiological response in the NAc is not unexpected, but the specificity of the identified biomarker presents an exciting therapeutic concept. The NAc is a central node in the mesocorticostriatal circuitry and is involved in all neurobiological stages of addiction[28]. Effects of disrupting the NAc activity with DBS were demonstrated in mouse models of relevant endophenotypes of SUD[29–32] and subsequently translated to off-label clinical application in humans[23,31,33,34]. A recent systematic review of DBS in addiction reported that the majority of 26 human studies (71 subjects) targeted the NAc for the treatment of various SUDs[6]. While efforts have been made in improving targeting with improved imaging techniques, none of the reported studies have yet utilized a biomarker-driven approach nor reported the use of a cue-reactivity task to optimize DBS therapy[35,36]. A recent perspective described the knowledge gap barriers to advancing this treatment, including the need for objective data to both guide programming and to improve understanding of addiction neurobiology[7]. While DBS for SUD remains investigational, our case study adds significant support to the potential feasibility of personalizing future SUD DBS therapy using craving-related electrographic biomarkers recorded in the NAc region.

Despite the constraints of the clinically-driven scenario in this patient, we observed an apparent relationship between the cue-reactive low frequency oscillations detected in the human NAc and self-reported cravings. Moreover, we demonstrated the feasibility of leveraging personalized biomarkers of cue-reactivity to guide optimization of DBS programming. In the past decade, interest in brain signal-based closed-loop neurostimulation has gained significant traction in movement disorders[37–40], epilepsy[41], and neuropsychiatric disorders[24,42,43]. This mode of stimulation is particularly intriguing for neuropsychiatric disorders that exhibit episodic and dynamic symptomatology[44], such as in SUD. In such conditions, chronic and continuous DBS may in fact result in tolerance or undesirable consequences such as blunting of normal physiological functions that utilize the same pathway[29–31]. Progress has been made in the pre-clinical setting in the identification of drug-related electrophysiological markers[45–48], but this has thus been limited in the clinical setting although there is significant promise and interest in the approach[49]. While the intent of this case study was not to inform a responsive, closed-loop stimulation strategy (in part due to limitations of the *in-situ* DBS system and the clinical nature of this intervention) the feasibility

of reprogramming the DBS system based on a behaviorally relevant electrophysiological biomarker, combined with the finding that transient stimulation periods acutely reduced corresponding clinical craving ratings, suggest the potential of using responsive neurostimulation to treat SUD. Finally, the overall charge density delivered was substantially reduced, suggesting further that this strategy may reduce adverse and untoward effects of DBS and provide a more durable solution that extends device lifespan.

We acknowledge the limitations of this N-of-1 case study, for which the results may not be broadly generalizable to SUD populations. However, we outline a compelling and promising utility of electrophysiological guidance to optimize DBS programming as well as to personalize this therapy. We propose this cue-reactive electrophysiological signal in the NAc shell region as a potential candidate disease biomarker that warrants further investigation in ongoing and future studies of DBS in SUD.

Figure 1

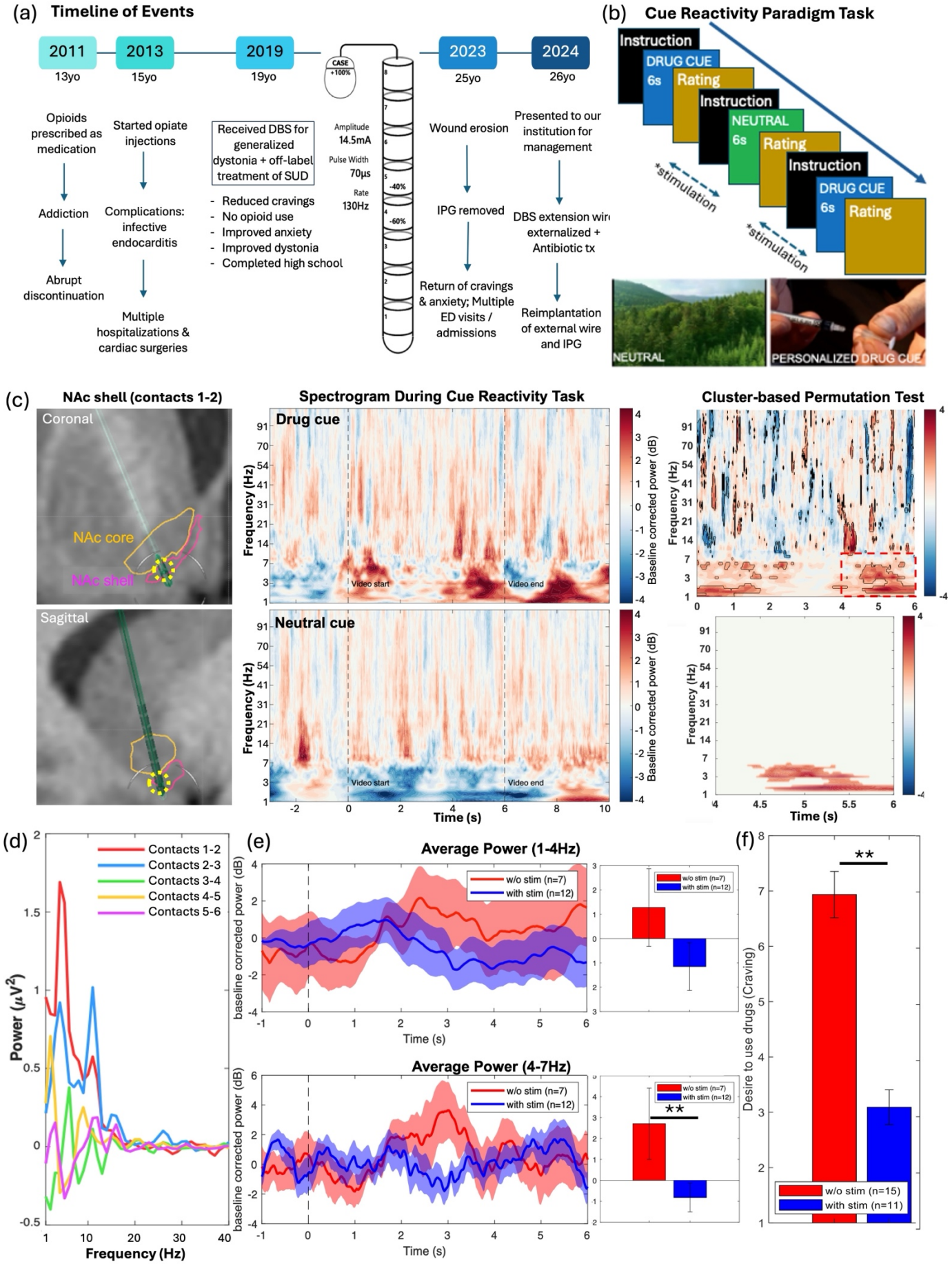
(a) Timeline of Events
2011
13yo
2013
15yo
2019
19yo
2023
25yo
2024
26yo
Opioids prescribed as medication
Addiction
Abrupt discontinuation
Started opiate injections
Complications: infective endocarditis
Multiple hospitalizations & cardiac surgeries
Received DBS for generalized dystonia + off-label treatment of SUD
- Reduced cravings
- No opioid use
- Improved anxiety
- Improved dystonia
- Completed high school
CASE +100%
Amplitude 14.5mA
Pulse Width 70µs
Rate 130Hz
-40%
-60%
Wound erosion
IPG removed
Return of cravings & anxiety; Multiple ED visits / admissions
Presented to our institution for management
DBS extension wire externalized + Antibiotic tx
Reimplantation of external wire and IPG
(b) Cue Reactivity Paradigm Task
Instruction
DRUG CUE 6s
Rating
Instruction
NEUTRAL 6s
Rating
Instruction
DRUG CUE 6s
Rating
*stimulation
*stimulation
NEUTRAL
PERSONALIZED DRUG CUE
(c) NAc shell (contacts 1-2)
Coronal
NAc core
NAc shell
Sagittal
Spectrogram During Cue Reactivity Task
Drug cue
Neutral cue
Frequency (Hz)
Baseline corrected power (dB)
Video start
Video end
Time (s)
Cluster-based Permutation Test
(d)
Contacts 1-2
Contacts 2-3
Contacts 3-4
Contacts 4-5
Contacts 5-6
Power (µV²)
Frequency (Hz)
(e)
Average Power (1-4Hz)
Average Power (4-7Hz)
w/o stim (n=7)
with stim (n=12)
baseline corrected power (dB)
Time (s)
**
(f)
Desire to use drugs (Craving)
w/o stim (n=15)
with stim (n=11)
**

Figure 1. A specific electrophysiological marker can be identified with a cue-reactivity paradigm task. (a) Timeline of events leading to subject presentation and evaluation for drug cue-reactivity. (b) Schematic of cue-reactivity paradigm task. Subject was presented with 6-seconds long videos in a quasi-random block design in two categories (drug cues and neutral; 12 repetitions). In stimulation trials, 10 minutes of stimulation was delivered prior to administration of the task, as well as intermittent stimulation (~15 seconds) before each cue was presented (*). (c) A specific low-frequency (1-7Hz) biomarker associated with drug cravings was identified in the nucleus accumbens (NAc) shell region. Left panel; Coronal (top) and sagittal (bottom) T1 MRI views of DBS electrode contacts (1-2) in the NAc. Yellow dotted circle demarcates contacts 1-2 where bipolar recordings were obtained. Middle panels; Time-frequency analysis (-3 to 10s) showed an increase in power in the low-frequency range when drug-related cues were presented (*Top*), as compared to neutral cues (*Bottom*). Right panel; Cluster analysis was used to identify time window and frequency ranges that were significantly different between drug cue and neutral cue trials (*Top*). Dotted red box denotes time window and cluster that survived permutation testings, showing a statistically significant increase in low frequency (1-7Hz) power spectrum upon presentation of drug-related cues (bottom). Similar time-frequency analysis did not identify any significant difference in power in LFPs recorded in other electrode contact pairs. (d) Power spectral density plot showing significantly elevated power in the 1-7Hz frequency band in contacts 1-2, but not in other electrode contact pairs. (e) Left; Distribution of average power of (*Top)* 1-4Hz frequency band and (*Bottom)* 1-7Hz frequency band across time, without stimulation (red) and with NAc shell stimulation (blue). Right; Bar chart shows corresponding difference in average power of the 1-4Hz (top) ($p=0.093$) and 4-7Hz (bottom) ($p=0.019$) frequency band was detected. (f) This was associated with a significant reduction in subjective ratings of cravings with stimulation turned on (blue bar) when compared to no stimulation (red bar). *LFP=local field potentials; MRI=magnetic resonance imaging; NAc=nucleus accumbens; vALIC=ventral anterior limb of the internal capsule*

Figure 2

(a) Acute stimulation monopolar assessment

1. Monopolar assessment – Identification of therapeutic and side-effect threshold

Stimulation Contacts	Anatomical Region	Best Parameters	Patient Report
1-/2+	NAc shell	5mA, 90us, 130Hz	No cravings (0/10); Improved mood and anxiety
2-/3+	NAc core	6mA, 90us, 130Hz	Reduced cravings (1/10); Improved anxiety level
3-/4+	NAc core	4mA, 90us, 130Hz	Mild reduction in cravings (2/10); Worsened mood.
4-/5+	vALIC	8mA, 90us, 130Hz	Reduced cravings (1/10); Improved mood and anxiety
5-/6+	vALIC	7mA, 90us, 130Hz	Reduced cravings (1/10); Mood slightly worsened
6-/7+	vALIC	5mA, 90us, 130Hz	Unpleasant dysphoria
7-/8+	ALIC	5mA, 90us, 130Hz	Sensation of overstimulation

2. Sham-controlled stimulation testing

Sham		-	Cravings 4/10
1-/2+	NAc shell	6mA, 90us, 130Hz	Cravings 1/10
Sham		-	Cravings 4/10
4-/5+	vALIC	7mA, 90us, 130Hz	Cravings 2/10

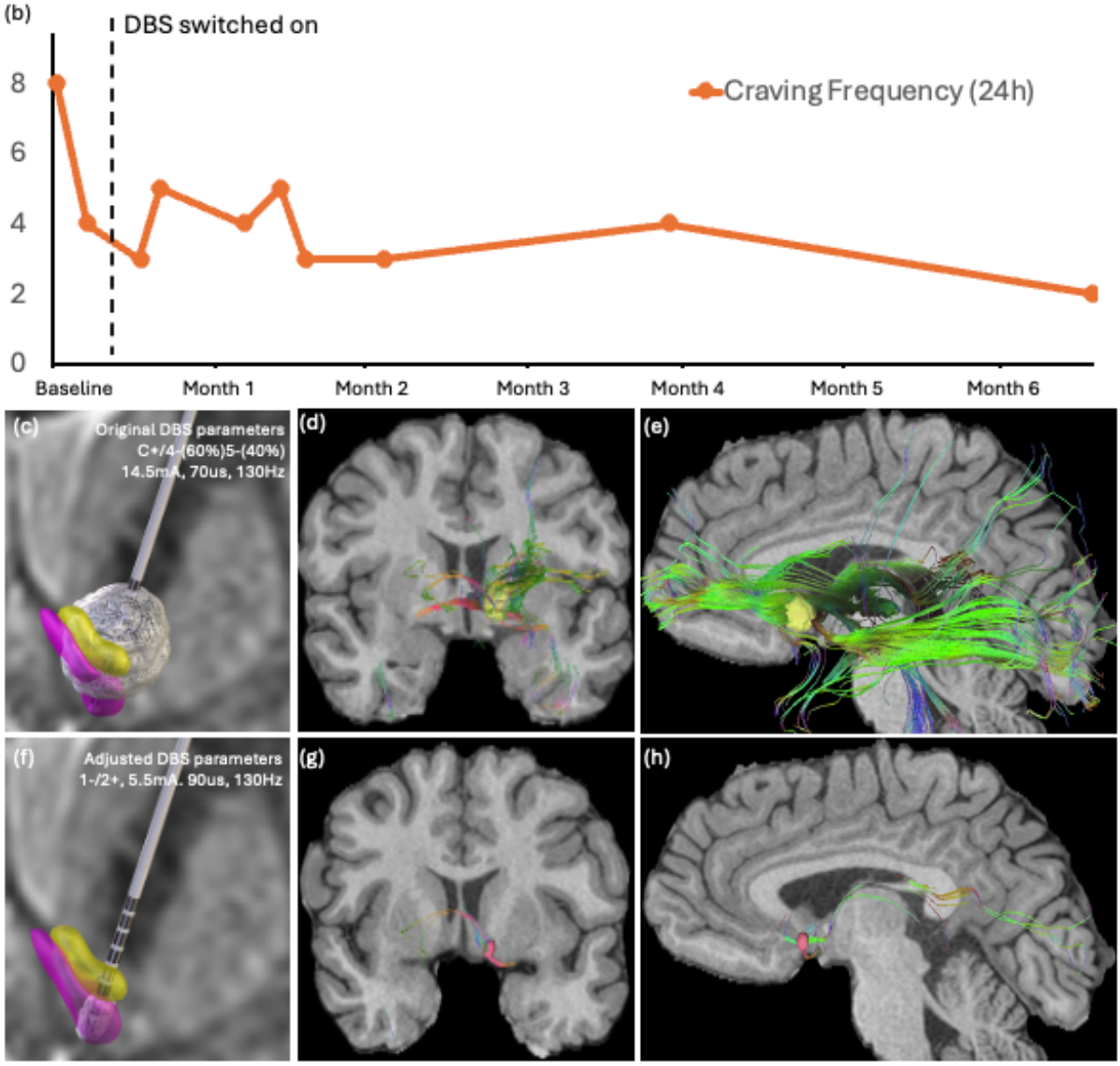

Figure 2. (a) Stimulation assessment corroborated optimal stimulation settings with electro-physiological findings in the NAc shell. (b) Continuous stimulation at 5.5mA (vs 14.5mA previously) achieved sustained reduction of craving intensity and frequency based on the Brief Substance Cravings Scale (BSCS) at 6 months. Volume of tissue activation (VTA) modelling based on finite-element modelling (FEM) and structural connectivity analysis based on (c-e) original DBS parameters (C+/4-(60%)5-(40%), 14.5mA, 70us, 130Hz) and (f-h) new DBS parameters (1-/2+, 5.5mA, 90us, 130Hz). Middle and right panels display coronal and sagittal view of structural connectivity of estimated VTAs to other brain regions. *DBS=deep brain stimulation; FEM=finite element method; NAc=nucleus accumbens; VTA=volume of tissue activation*

Online Methods

1. Prior Clinical History

   At the time of the current presentation, the subject was a 26-year old male with DBS implanted 4.5 years prior. He first developed an addiction to opioids from thirteen years old following rapid withdrawal of prescription opioid medication. He started intravenous use of opiates at age fifteen, and developed multiple complications of intravenous infections, including infective endocarditis that required five cardiac surgeries for valve replacement. He also had co-morbid severe bipolar disorder from age 10-11, and was treated with multiple anti-depressants, mood stabilizers and anti-psychotic medications. He subsequently developed disabling tardive dystonia that disrupted all his activities of daily living. He was referred by his neurologist and psychiatrist for off-label bilateral DBS of the globus pallidus interna (GPI) to treat his severe tardive dystonia[14]. At the same time, discussions were made for DBS therapy for his severe, medication-refractory OUD. Upon discussion with patient, his parents and careful consideration of potential risks and benefits, a consensus decision was made for bilateral GPi DBS (with right-sided implantable pulse generator, IPG), as well as a unilateral left NAc DBS (left-sided IPG) (Fig S1).

   The DBS was programmed based on clinical monopolar assessment per standard practice in movement disorders. The bilateral GPI DBS treatment improved his tardive dystonia significantly, which remained stable with minimal adjustment required since initiation. Left NAc DBS electrode was optimized based on clinical assessment, but required a very high dose of stimulation (14.5mA) between contacts 4 and 5, which were located in the ventral anterior limb of the internal capsule (vALIC) (Fig S1c). This resulted in rapid charge depletion of the IPG. Unfortunately, he was unable to tolerate a rechargeable system, which destabilized his clinical condition whenever the IPG was inadequately charged, leading to the team to recommend switching to non-rechargeable IPGs. Several months after DBS implantation, he relocated to France, where a local psychiatrist managed his condition and DBS programming, and he was lost-to-follow-up. A subsequent wound erosion over the left subclavicular incision led to the removal of the left DBS IPG, which was followed by rapid return of his opioid cravings within the first weeks, which were uncommon when DBS system was working (Fig 1a). He then reached out to our institution for further management because he feared high risk for relapse to OUD with return of his opioid cravings.

   There were several concerns in the management of this patient. First, a time-sensitive restoration of his DBS therapy was considered to be crucial, as he had demonstrated good and stable response to DBS therapy, and discontinuation of DBS therapy may lead to OUD relapse and destabilization of his psychiatric conditions, including risks of suicide. Second, the high charge requirement and intolerance of a rechargeable system was worrisome in view of his young age. Thirdly, it was crucial to ensure complete eradication of infective organism before re-implantation of the IPG due to risk to both the DBS device as well as his prosthetic heart valves. With these considerations in mind, the patient was hospitalized for treatment, with a motivation to restore his DBS therapy as soon as safely possible and potentially optimize programming parameters. A wound swab revealed persistence of Staphylococcus aureus in the left chest pocket. Upon consultation with infectious disease specialist, he was commenced on intravenous antibiotics and the DBS system was externalized with an extension wire in an attempt to preserve the proximal system while antibiotic treatment ensued. During this time, we devised a plan to use personalized computer-based cue-reactivity tasks to attempt to identify potential electrophysiological biomarker of drug cue-reactivity in order to localize the most active node encompassed by the NAc electrode[10]. We hypothesized that prior high amplitude requirements were due to non-specific stimulation target engagement and that a more precise stimulation may help reduce charge requirement and extend device lifespan which would be critical in the management of this patient.

2. Computer-based Tasks

   (a) Personalized cue-reactivity paradigm task. The subject was interviewed for specific details related to his drug use habits and preferences prior to the task. The cue-reactivity paradigm task involves use of personalized 6-second video cues presented to the subject in a quasi-random block design in two categories (drug cues and neutral cues). The subject was asked to rate his level of craving from 1 (no

craving) to 9 (extremely high craving) after each cue presentation. Twelve repetitions of each condition were conducted to allow for comparison of responses to identify differences in electrophysiological responses to drug cues and neutral cues.

(b) Monetary-Incentive Delay (MID) task[15]. The MID task is a validated and widely-used cognitive task to identify neural substrates of monetary reward anticipation and outcome. The subject was presented with a visual shape cue that signals the possibility of a reward (potential gain), loss (potential loss) or neutral (no gain or loss) trial. Following a cue presentation of two seconds, a delay phase of two seconds is present before a target appears to prompt a response by the subject with a button press as quickly as possible to gain the reward or avoid a loss. Finally, in the feedback/outcome phase, the subject receives performance feedback with cumulative earnings.

(c) Urge-for-action Task (UFAT)[16]. This task uses eyeblink suppression as a model for sensory-based urges, with blocks of free blinking (30-seconds) alternating with longer blink suppression periods (60-seconds). During the free blinking periods, the instruction 'Normal' is displayed and subject is allowed to blink as normal. During the blink suppression period, the instruction 'Hold' is displayed and subject is told to withhold blinking as long as the instruction is present. After this block, there is a recovery period with instruction 'Ok to blink' where the subject is allowed to blink as much as he wished, and a visual-analog-scale (VAS) rating of the urge to blink during the 'hold' period is collected. Eight blocks of each period are presented.

3. Electrophysiological Recording and Signal Analysis

A Boston Scientific DBS extension wire was tunneled and externalized after explant of the pulse generator to allow intravenous antibiotic treatment of the wound infection and preservation of the remaining DBS system. An in-house customized adapter was used to connect to the Boston Scientific DBS extension wire (Boston Scientific, Marlborough, MA) to the g.HIAMP PRO system (g.tec medical engineering GmbH, Austria) for continuous intracranial electroencephalographic (iEEG) local field potential (LFP) signal recordings through the in-situ Boston Scientific DB-2201 8-ringed contacts DBS electrode during conduct of the computer-based tasks.

Raw LFP data acquired at 1200Hz sampling rate was exported post-hoc for offline analysis using custom MATLAB scripts, applying a high-pass filter (1Hz) and notch filter at line noise frequency (58-62Hz) and harmonics. A time-frequency analysis using multi-taper wavelet convolution methods was used to characterize spectral power components of the cue-reactive signals. The power was extracted by squaring the magnitude of the complex Fourier-spectra and transformed by the log function. The time window length was shortened (3 to 0.13s) with increase in frequency (1-115Hz) with time step of 0.02s. The frequency resolution was dense in the low frequencies starting from 1Hz and more sparse in the high frequencies up to 115Hz using log space. The power spectrum was baseline corrected using the interval 0.1-1sec before the cue using a common baseline for all trials. Difference in mean power spectrogram obtained from each condition epoch (e.g., drug-cue or blink suppression) is compared to a neutral condition epoch (e.g., neutral-cue or normal blink) which acts as control condition, and is then calculated for statistical significance (independent sample t-test and cluster-based permutation approach) to identify the candidate biomarker. This was systematically performed for different frequency bands ranging from 1-115 Hz, with different size ranges, e.g., band power from 1-4 Hz and band power from 1-12 Hz.

4. Neuroimaging Analyses

High resolution pre-operative MRI and post-operative CT head were available for imaging analyses. T1, T2, and fast gray matter acquisition T1 inversion recovery (FGATIR) sequences were acquired at 1mm thick slices on a 3T GE scanner (GE Healthcare, Chicago, IL), as well as multi-shell 64-directions diffusion weighted imaging for tractography. The post-operative CT was co-registered to the pre-operative MRI using a 2-step linear and non-linear registration using Advanced Normalization Tools[50]. Probabilistic tractography was performed using FMRIB Software Library (FSL)'s Probtrackx2 using the NAc as a seed and the

subgenual cortex as a target to subsegment the NAc into shell and core regions using clustering of streamline density according to our previously published methods[18].

Volume-of-tissue activation (VTA) analysis was performed using Lead-DBS software based on active DBS parameters using its in-built finite element modeling (FEM)[51]. Structural connectivity analysis with streamlines was performed using the DSI-Studio[52] using the estimated VTAs as seeds in the whole brain tractography derived from patient's diffusion MRI.

5. Stimulation Testing

Using the Boston Scientific external stimulator, a systematic monopolar assessment was performed across adjacent electrode contact pairs. Acute stimulation effects were recorded and assessed for therapeutic as well as side-effect thresholds. To confirm effects of stimulation, a short sham-controlled stimulation session was conducted to verify the effects of active stimulation.

6. Clinical Outcomes

The Brief Substance Craving Scale (BSCS) and Brief Addiction Monitor (BAM) questionnaires were administered to trend the levels of cravings as well as substance use over time.

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