Closing the loop on impulsivity via nucleus accumbens delta-band activity in mice and man

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Reward hypersensitization is a common feature of neuropsychiatric disorders, manifesting as impulsivity for anticipated incentives. Temporally specific changes in activity within the nucleus accumbens (NAc), which occur during anticipatory periods preceding consummatory behavior, represent a critical opportunity for intervention. However, no available therapy is capable of automatically sensing and therapeutically responding to this vulnerable moment in time when anticipation-related neural signals may be present. To identify translatable biomarkers for an off-the-shelf responsive neurostimulation system, we record local field potentials from the NAc of mice and a human anticipating conventional rewards. We find increased power in 1- to 4-Hz oscillations predominate during reward anticipation, which can effectively trigger neurostimulation that reduces consummatory behavior in mice sensitized to highly palatable food. Similar oscillations are present in human NAc during reward anticipation, highlighting the translational potential of our findings in the development of a treatment for a major unmet need.

Deep brain stimulation | nucleus accumbens | delta band | closed loop | reward

Impulsivity is one of the most pervasive and disabling features common to many disorders of the brain (1–3). Heightened responsivity in the nucleus accumbens (NAc) during anticipation of a rewarding stimulus predisposes to impulsive behavior, which can have severe implications for development of maladaptive behaviors (4–8). Notably, electrophysiological, neurochemical, and functional neuroimaging correlates have been reported in multiple species during brief windows of anticipation (5, 9–13). These correlates (or biomarkers) that precede a “moment of weakness” have potential to inform a therapeutic to deliver a time-sensitive intervention.

Recently, a responsive neurostimulation (RNS) system was approved by the US Food and Drug Administration for adjunctive treatment of partial onset seizures (14). This intracranial closed-loop system has proven capable of detecting epileptiform activity and preventing propagation by responsively delivering electrical stimulation directly to the seizure onset zone. Here, we examine the potential for RNS to intervene during a vulnerable period immediately preceding receipt of highly rewarding stimuli, an undertaking that has immediate translational potential given the availability of this system. We leveraged the finding that electrically stimulating the NAc in mice anticipating a food reward effectively attenuates binge-eating behavior (15). To “close the loop” on this intervention using an automatic stimulatory system, however, the identification, characterization, and refinement of an anticipatory biomarker are critical next steps.

Given that the currently approved RNS system is limited to local field potential (LFP) recordings due to its implanted depth macroelectrodes’ spatial resolution, we make LFP recordings from the mouse and human NAc during a period of reward anticipation, and find prominent delta oscillations elicited during anticipation of a highly rewarding stimulus. Multiunit analysis reveals strong correlations between delta oscillations and unit activities in the NAc. Utilizing this translational biomarker as a trigger, RNS blocked binge eating in mice with remarkable behavioral specificity, thereby taking the first critical step toward the development of a targeted intervention for neuropsychiatric patients suffering from hypersensitivity to pathological motivations.

Results

Increase in NAc Delta-Range Field Potentials Precedes Binge Eating in Mice. Multielectrode arrays were implanted into the NAc of mice \((n = 6)\) (Fig. 1 A–D). Following a 1-wk recovery period, these mice were put on a protocol of 1-h daily exposure to high fat (HF) (standard house chow ad libitum) known to induce binge-like eating behavior (defined as consumption of >25% of daily caloric intake from HF; Fig. 1 E–G). Given prior reports across species of changes in NAc cell firing during reward anticipation (13, 16, 17), mouse NAc LFPs were recorded daily for 2 h, 1 h before and 1 h during exposure to HF food. All mice reached criterion for stable binge eating by day 10 (<10% variation across 3 consecutive days) (15). Power spectral density analyses of NAc LFPs averaged across mice immediately before HF intake on days 0 and 10 were carried out. As a control, identical analyses were performed immediately before the mice ingested standard chow (Fig. 2 A–C). Because our goal was to interrupt a brief vulnerable window in time immediately before a pathological impulse such as a binge-eating episode, we used 2-s windows across a 4-s epoch, which covered from 2 s before to 2 s after the onset of a binge.

Significance

We reveal prominent delta oscillations in the nucleus accumbens preceding food reward in mice and use them to guide responsive neurostimulation to suppress binge-like behavior. Similar electrographic signatures are observed in human nucleus accumbens during reward anticipation as well, suggesting their translational potential in the development of a treatment for loss of impulse control in obesity and perhaps additional brain disorders.


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The most robust change in LFPs was increased power in very-low-frequency (delta) oscillations once binge eating developed on day 10 immediately before HF intake (Fig. 2 D–H). Mean time–frequency spectograms and comparison of individual frequency bands (delta, 1–4 Hz; alpha, 4–8 Hz; theta, 8–12 Hz; beta, 12–30 Hz; gamma, 30–50 Hz) confirmed that the only statistically significant change in spectral power occurred in the delta frequency range immediately before HF intake after the development of binge-like behavior, compared with baseline (day 0) HF and chow control (delta: $F = 6.165$, $P < 0.001$; Tukey’s post hoc test: chow vs. day 0 HF, n.s.; chow vs. day 10 HF, $P < 0.01$; day 0 HF vs. day 10 HF, $P < 0.01$: Fig. 2H; alpha, theta, beta, and gamma, chow vs. day 10 HF, n.s.). This increase in power in the delta range was not detected immediately before chow intake, suggesting it was not related to movement or bite artifact. (Movie S1 illustrates increased power in the delta band during HF intake.)

We next compared the delta power immediately before HF consumption on day 10 with that during the entire 1-h exposure to HF. NAc delta oscillations normalized to the entire 1-h period of HF exposure revealed a 30% increase in power during the 2-s window before onset of HF consumption (Fig. 2I). Analysis of delta power peak distribution revealed a peak at $\sim 1$ s before the onset of HF consumption (Fig. 2J). To further test whether the increase in delta power was specific for this highly appetitive food, we recorded LFPs immediately before the interaction of the experimental mice with a novel juvenile, an appetitive experience with a finite, definable onset (Fig. 2K). Delta power was significantly lower before the onset of juvenile interaction.
compared with the time period before onset of HF intake \(T_{(5)} = 2.719, P < 0.05; \text{Fig. S1} \). Together, these results suggest that an increase in delta power in LFPs recorded from the NAc precede intake of HF in binge-eating mice and therefore may be a useful biomarker to trigger RNS.

**Delta Oscillations as a Biomarker for RNS.** Based on the previous findings, we assessed whether a delta-power threshold could serve as a biomarker to optimize RNS to attenuate HF intake in mice. The closed-loop system (Fig. 2F) was set to trigger whenever delta power exceeded a predefined threshold based on delta peak distribution and power analyses (a threshold of 20% higher than baseline delta power was used, or 1 SD below the mean power immediately before the onset of HF intake; Fig. 2F). When this threshold was reached, electrodes delivered a bipolar, biphasic, 0.1-mA stimulation at 130 Hz for 10 s (Fig. 3A). We compared the efficacy of RNS with that of other neurostimulation protocols in the same experimental animals. Specifically, we also tested (i) continuous electrical stimulation during the entire 1-h exposure to HF, a pattern of stimulation commonly referred to as deep brain stimulation (DBS) (130 Hz, 0.1 mA, bipolar, biphasic); (ii) manually triggered stimulation during which an experimenter remotely observed the subjects’ behavior via video monitoring and triggered electrical stimulation (130 Hz, 0.1 mA, 10 s, bipolar, biphasic stimulation) at the immediate onset of HF consumption; and (iii) random stimulation during which bouts of stimulation (130 Hz, 0.1 mA, 10 s, bipolar, biphasic stimulation) were delivered randomly throughout the entire 1-h HF exposure such that the total number of stimulation bouts matched that delivered during the RNS protocols.

To ensure that caloric intake from HF returned to baseline immediately after the stimulation days, each session was followed by a stimulation-off period (Fig. 3B). All of the stimulation protocols significantly reduced HF intake except random stimulation \[Fig. 3 \text{C–F}; DBS T_{(5)} = 2.58, P < 0.05; manual T_{(5)} = 3.75, P < 0.05; \] RNS \[T_{(5)} = 4.29, P < 0.01; \text{random} T_{(5)} = 0.62, P = 0.56 \]. At the end of each of these experiments, we repeated another session of RNS, which reproduced the previously seen significant decrease in HF intake \(T_{(5)} = 3.999, P < 0.01; \text{Fig. S2A} \). We compared the reduction of HF intake between each stimulation protocol and found that the reductions in HF intake induced by manual stimulation and RNS were significantly more robust than random stimulation \[sphericity assumed, \(F_{(4)} = 7.034, P < 0.01; \text{post hoc} \); Manual vs. Random, \(P = 0.042; \] RNS vs. Random, \(P = 0.029; \] DBS vs. Random, DBS vs. Manual, DBS vs. RNS, Manual vs. RNS, n.s., Bonferroni corrected; \text{Fig. 3G} \]. Furthermore, the number of stimulation bouts used for manual stimulation \(P < 0.05\) was significantly lower than \(DBS_{(5)} = 65.80, P < 0.0001; \text{post hoc} \); DBS vs. Manual, \(P < 0.0001; \] DBS vs. RNS, \(P < 0.0001; \] RNS vs. Manual, n.s.; Tukey’s correction applied; \text{Fig. 3H} \). \text{(Movie S2 demonstrates RNS triggered by increased delta oscillations before HF intake.)}
0 HF, n.s.; chow vs. day 10 HF, P < 0.05; day 0 HF vs. day 10 HF, P < 0.05; Tukey corrected; Fig. 4 D and E]. Last, the spike rate significantly correlated with delta power on day 10 immediately before and during HF consumption (Pearson r = 0.50, P < 0.0001; Fig. 4F).

fMRI Activity and Delta Oscillations in Human NAc During Reward Anticipation. To evaluate the translational potential of delta-range field potentials providing physiologic real-time optimization for RNS in human patients suffering from impulsivity, we recorded intraoperative LFPs from the NAc in a human subject suffering from intractable obsessive-compulsive disorder during a period of reward anticipation analogous to the phase of food reward anticipation examined in mice. Specifically, because in the operating room food rewards could not be provided, we instead elicited anticipation of monetary rewards with a well-established neuroimaging task [i.e., the monetary incentive delay (MID) task]. During each trial of the MID task, a subject sees a visual cue indicating that they will gain or avoid losing an indicated monetary incentive (reward or punishment) by subsequently pressing a button in response to a rapidly presented target. This task allows researchers to distinguish neural responses during different stages of reward processing, including reward anticipation and outcomes (10) (Fig. 5).

Before surgery during a diagnostic magnetic resonance imaging (MRI) scan, fMRI revealed a significant increase in blood oxygen level-dependent (BOLD) signal in the NAc during anticipation of high monetary reward [high reward:baseline, T(17) = 3.23, P < 0.01, uncorrected; low reward:baseline, high punishment:baseline, low punishment:baseline, n.s.; Fig. 5 B and C; summary of head movement shown in Fig. S3, demonstrating <1 mm of head movement]. This finding replicated previous reports using normal subjects and corroborates a well-established involvement of the human NAc during reward anticipation (18). LFPs were recorded via an implanted quadrupolar electrode (3389; Medtronic) in the NAc, the location of which was defined by merging a postoperative computed tomography scan of the head to a preoperative 7-T MRI scan using gray matter nulled by merging a postoperative computed tomography scan of the head to a preoperative 7-T MRI scan using gray matter null sequences that indicate precise white matter–gray matter boundaries (Fig. 5D). Power spectral density analysis of NAc LFPs during no reward and high reward anticipation (Fig. 5 E–H) revealed an increase in delta power during the anticipation period for high reward compared with no reward in the most ventral channel [Fig. 5H: F(4,67) = 3.514, P < 0.05, post hoc: high reward vs. baseline, P < 0.01; Tukey’s correction applied]. Head and limb movement during intraoperative LFP recordings (Fig. S3B) indicated that there was very little detectable movement. Comparison of delta-power measurements during anticipation of high punishments, low punishments, and low rewards normalized to baseline revealed significant increase during anticipation of high reward vs. low punishment (Fig. 5I and Fig. S4). We also investigated the correlation between NAc LFP and unit activity during MID task, and found selective phase-locking of spikes to the peak (phase 0) of the delta (2- to 3-Hz) oscillations (Fig. S5).

Discussion

We have demonstrated that anticipation of a large, HF food reward increases delta oscillatory power in the NAc in mice, and preliminary findings from a single human subject support the translatability of this potential biomarker for RNS. In sated mice exhibiting binge-eating behavior, strong delta oscillations are detected 2 s before consuming food reward, but not before intake of house chow. This increase in delta power is not observed before or during general locomotor behavior or social interaction, and is positively correlated with unit activity in the NAc. Using a threshold in delta-band power as a biomarker to trigger delivery of a brief train of high-frequency electrical stimulation pulses to the NAc resulted in significant attenuation...
of HF intake. The effectiveness of this RNS was reproducible and behaviorally specific. Namely, utilizing power in the delta band as a trigger for RNS did not interfere with social interaction or locomotor behaviors. Moreover, the number of stimulation bouts delivered during RNS was significantly lower than DBS to achieve the same reduction in HF intake. Stimulation of the NAc was not reinforcing or aversive as assayed by a real-time place preference protocol, suggesting that stimulation-induced blockade of HF intake was not substituting for the anticipated food reward or inducing an aversion. Post hoc review of stimulations triggered during RNS revealed that our biomarker settings correctly anticipated about two-thirds of HF binge onsets, while approximately one-quarter of the triggered stimulations were not associated with subsequent binge onset.

To examine the translational potential of our findings, we analyzed NAc LFPs during anticipation of monetary rewards in a human subject, which, like HF in mice, demonstrably elicits vigorous approach (10). The MID task was used here so that we could examine the human NAc LFPs during a similar brief period of reward anticipation that was studied in mice. Anticipation of large financial incentives are known to reliably increase NAc BOLD signal activity in healthy individuals (18). Because BOLD activity has been reported to correlate with changes in LFPs (19, 20), we predicted that anticipation of large rewards would induce measurable changes in LFPs in the NAc. Consistent with what is commonly observed in healthy individuals, event-related fMRI in a human subject suffering from severe obsessive-compulsive disorder revealed increased NAc BOLD signal during anticipation of large rewards. Most importantly, NAc LFPs recorded from this subject exhibited an increase in power in the delta band during anticipation of high monetary rewards. These electrophysiological changes echoed those seen in mice anticipating HF reward and importantly were detected by a clinically approved benchtop system. Moreover, the MID task is a good probe of physiological changes echoed those seen in mice anticipating HF reward and importantly was detected by a clinically approved benchtop system. Moreover, the MID task is a good probe of physiological changes echoed those seen in mice anticipating HF reward and importantly was detected by a clinically approved benchtop system.

Fig. 5. Schematic of functional neuroimaging and local field potentials (LFPs) recording during the monetary incentive delay (MID) task in human subject. (A) Schematic of the MID task, which consists of cue onset, anticipation phase, target onset, and outcome phase. (B) Functional magnetic resonance imaging (fMRI) showing area activated by gain vs. nongain anticipation in the nucleus accumbens (NAc) (white circle; Z > 2.54; cluster, four 3-mm cubic voxels). (C) Blood oxygen level-dependent (BOLD) signal changes during MID task extracted from activated voxels in the left NAc averaged by condition, indicating NAc activation during high reward anticipation compared with baseline [high reward: baseline, TR(17) = 3.23, P < 0.01, uncorrected; low reward: baseline, high punishment: baseline, low punishment: baseline, n.s.]. (D) Electrode contact locations in the NAc for LFP recording using preoperative 7-T MRI merged with postoperative computed tomography scan. Coronal view (trajectory view not shown) demonstrates most posterior aspect of electrode trajectory with the following entry anterior-posterior commissure coordinates: x = 41.31, y = 43.39, z = 43.59; 34.2° from midsagittal plane; 60.3° from axial plane. (E) Coordinates for the ventral-most extent of the recording lead: x = 6.03, y = 15.07, z = −6.60. The measurement of 7.5 mm indicates the span of the lead. (F and G) Raw LFPs during baseline and anticipation of high reward. (H) Power density analysis revealing significant increase in delta power during anticipation of high reward compared with baseline. (J) Normalized NAc LFP power spectogram (averaged across individual trials), indicating increased delta band (1- to 4-Hz) power during anticipation of high reward (insets: frequency range from 0 to 50 Hz). *P < 0.01. BL, baseline; HP, high punishment; HR, high reward; LP, low punishment; LR, low reward. See also Figs. S3–S5.

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smaller scale LFP measured by the microelectrode. However, the
finding of spike–field coupling does establish the saliency of the
delta-range power as a marker of local computation. Together,
these findings demonstrate that NAc LFPs carry information
relevant to reward anticipation and cue sensitivity, and provide the
potential to be used as a neural electrographic biomarker to guide RNS treatment for
neuropsychiatric disorders exhibiting impulsivity.

RNS remains a therapeutic approach with which clinicians have limited experience. For intratable temporal lobe epilepsy, RNS has proven efficacious in reducing seizure frequency and severity with outcomes that are not only durable but also improve over time (25). Several lines of evidence also suggest that responsive or closed-loop DBS using power in the beta band detected in the subthalamic nucleus across species may be super-
ior to traditional continuous DBS for Parkinson’s disease treatment (26–29). Moreover, closed-loop neurostimulation strategies have exhibited promise for other neuropsychiatric
diseases, demonstrating the broad potential for this line of re-
search (30).

Our findings provide preliminary evidence that RNS has po-
tential for treating intractable behavioral disorders that have not previously been considered optimal candidates for neurosurgical approaches, including eating disorders, and even obesity and addiction. Undoubtedly, further work will optimize biomarkers of reward anticipation by improving their specificity and sensitivity. We used chow as the primary food control in our study, and social activity as another behavioral control as this is considered an assay of reward processing in mice. The conse-
quences of exposure to other appetitive stimuli, such as drugs of abuse or sexually receptive partners, will be important to ex-
amine to better define the specificity of the LFP biomarkers reported here. Clearly, many more experiments in both animals and humans will be necessary to minimize potential side effects of RNS and maximize its therapeutic utility. Nevertheless, the fact that mouse and human NAc LFPs exhibit similar changes during reward anticipation suggests that mechanistically driven research in rodents can inform what is eventually done in human subjects. Furthermore, we have demonstrated that the candidate biomarker can be detected using an off-the-shelf, commercially available RNS device, suggesting that rapid progress can be made toward a neurostimulation treatment for patients suffering from intractable, life-threatening impulse control disorders. As human trials are undertaken for novel behavioral indications, systematic plans for monitoring patient subjects by a multidisci-
plinary team will be critical to best assay the future potential of this intervention.

Materials and Methods

All animal procedures conformed to the NIH Guide for the Care and Use of Laboratory Animals (31) and were approved by the Stanford University Administrative Panel on Laboratory Animal Care (APLAC-30216). Clinical investigation was carried out in accordance with a Stanford University IRB-approved protocol (IRB-33146). Informed consent was obtained. See SI Materials and Methods for details.

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**Supporting Information**

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**SI Materials and Methods**

**Animal Studies.**

**Animals.** All mice were male C57BL/6J (8 wk) purchased from The Jackson Laboratory. Mice were individually housed on a 12-h light/dark schedule and were sated with food and water ad libitum. House chow contained 18.6% protein, 44.2% carbohydrates, and 6.2% fat by calories and 3.10 kcal/g (Teklad Diet). Given a previously validated model of binge-eating behavior using limited exposure to a very high-fat (HF) diet protocol, a diet which contained 20% protein, 20% carbohydrates, and 60% fat by calories and 5.24 kcal/g (Research Diets) was used in this study to model binge-eating (1). All procedures conformed to the NIH Guide for the Care and Use of Laboratory Animals (2) and were approved by the Stanford University Administrative Panel on Laboratory Animal Care (APLAC-30216).

**Surgery and histology.** After 1 wk of habituation to our facility, mice were anesthetized with ketamine/xylazine and mounted in a stereotaxic frame (Kopf Instruments). Custom multipole electrode arrays (70/30% Pt/Ir, 125 μm; Microprobes) were implanted unilaterally into the left NAc, according to the following coordinates relative to bregma: 1.34 mm anterior, 0.60 mm lateral, and 4.25 mm deep to brain surface (3). Skull screws overlying the frontal cortex served as reference. At the end of our behavioral protocol, mice were anesthetized with pentobarbital and perfused transcaldicularly with 4% paraformaldehyde fixative. Electrodes were then removed. Whole brains were extracted from the crania, postfixed for 24 h, and submerged in PBS for 48 h. Brains were cut by microtome into 60-μm coronal sections and examined under a confocal microscope to verify electrode placement.

**Behavioral assays.**

**Binge-eating behavior.** Binge eating, defined here as consumption of 25% or more of the daily caloric intake with a 1-h binge episode, was observed in all mice using a limited-access protocol. This protocol is known to induce binge-like behavior in noncalorically restricted mice because of the brevity and intermittent nature of the exposure (1). A single, preweighed HF pellet was provided to the mice in their home cage daily for 1 h. Intake of the HF diet within that 1-h period was measured, as was 24-h consumption of house chow. Stimulation protocols were only initiated following 3 d of stable binge eating (<10% variation across 3 consecutive days). Consumption of chow and HF were recorded with time stamp via a CCD camera interfaced with Ethovision software (Noldus).

**Juvenile interaction test.** Novel male C57BL/6J (4 wk) mice purchased from The Jackson Laboratory were used as the juvenile mice. Open-field arenas and the video-tracking apparatus and software (Ethovision; Noldus) were set up to monitor behavior (4). Experimental mice were habituated to the testing suite for ~1 h before testing. Each juvenile interaction test is composed of two 150-s phases either with or without NAc stimulation (Electrical stimulation) separated by a duration of 30 s. Immediately after terminating phase 1, we removed the test mouse from the arena and returned it to its home cage until phase 2. The test mouse encountered a novel juvenile mouse during each phase.

**Real-time placed preference test.** Mice were placed in a custom-made three-chamber behavioral arena (75 × 25 × 25-cm black Plexiglas) for 30 min (5). One side of the chamber (30 × 25 cm) was assigned as the continuous stimulation side and the other as nonstimulation (30 × 25 cm). At the start of the session, mice were placed in the center chamber (15 × 25 cm). Every time the mice crossed to the stimulation chamber, electrical stimulation was delivered to the NAc until the mice crossed back into the center chamber. Percentage of time spent on the stimulation-paired and movement were recorded via a CCD camera interfaced with Ethovision software (Noldus).

**Behavioral and neural signal recording and analyses.** During all of the behavioral assays, mice were tethered to a neural recording device (AlphaLab SnR; Alpha Omega), and neural signals were recorded at 22 kHz continuously, together with synchronized behavioral data (Ethovision; Noldus). To extract information in the LFP range, signals were down-sampled off-line to 1,375 Hz, and segments corresponding to chow and HF intake (during exposure to HF) and juvenile interaction (in juvenile interaction test) were extracted (2-s epoch before the onset of the task). The short-time Fourier transform was used to approximate the power spectrum (Welch’s method, window of 1 s, 50% overlap) and averaged across individual mice (6). Time-frequency domain analysis was performed using a short-time Fourier transform of a 1-s sliding window and 90% overlap (averaged across individual mice). For multunit analysis, raw signals were analyzed using the Wave Clus toolbox (7). Signal processing was performed using the MatLab software package and custom scripts. Behavioral analyses were performed manually (examiner blinded) for identification of the onsets of chow and HF consumptions and juvenile interaction, and using EthoVision (Noldus) for place preference test.

**Electrical stimulation.** Electrical stimulation (0.1 mA, 130 Hz, biphasic, 90 μs) was used throughout different behavioral assays. Electrical stimulation was applied continuously to mimic DBS conditions. In the manual setting during HF exposure, electrical stimulation was turned on for 10 s by an experimenter (H.W.) remotely as soon as HF consumption was observed, and then turned off until the next binge-like behavior was observed. In the RNS setting, stimulation was triggered by a programmable biomarker detector (Neurostimulator; model RNS-300; Neuropace), in which the biomarker detection could be set up by predefining window size, minimum width, count criterion, minimum amplitude, bandpass hysteresis, and bandpass threshold. A typical biomarker detection setup for the delta oscillations was as follows: 1,200-ms window size, count criterion = 4, bandpass hysteresis = 255, bandpass threshold = 3, and 20% increase delta power. In randomly applied stimulation setting during HF exposure, electrical stimulation was administered according to a predefined randomized protocol.

**Statistics.** Student’s t test was used to determine statistical differences for chow and HF intake, spectral power during chow and HF intake, and real-time place preference. One-way ANOVA was used to determine statistical differences for power consumption, juvenile interaction, locomotor, and spectral power during MID task. Repeated-measures ANOVA was used to determine statistical differences for reduction in HF intake induced by different stimulation protocols. Bonferroni post hoc analysis was applied, when necessary, to correct for multiple comparisons. Statistical significance was *P < 0.05, **P < 0.01, and ***P < 0.001. All data values are presented as means ± SEM. We used SPSS 21 (IBM) for all statistical analyses.

**Human Studies.**

**Participant data.** The human subject was a 64-y-old male undergoing implantation of DBS electrodes in the NAc for treatment-resistant obsessive-compulsive disorder. The patient participated voluntarily in this two-part study after informed consent was obtained during preoperative consultation for the surgery, and was free to withdraw from the study at any time, including during imaging and surgery without consequence to clinical care. As per the protocol, the patient’s medications were...
continued before surgery. This investigation was carried out in accordance with a Stanford University IRB-approved protocol (IRB-33146). Informed consent was obtained. Preoperatively, this patient underwent a routine stereotactic magnetic resonance imaging (MRI) treatment planning protocol complemented by an ultra-high-field MRI (7-T) scan for visualizing precise NAc borders, and functional MRI (fMRI) (3-T) scanning during the monetary incentive delay (MID) task.

**MID task.** Before entering the fMRI scanner, this participant completed a practice version of a previously validated fMRI paradigm that elicits anticipation of monetary reward called the MID task. This practice task both minimized later learning effects and produced an estimate of each individual’s reaction time for standardizing task difficulty in the scanner. The participant was also shown the money that he could earn by performing the task successfully, and correctly believed that he would receive money at the end of the study period as a function of performance. Once in the scanner, anatomical and functional scans were collected, and the subject participated in one 42-min session in which the MID task occurred between a preliminary 144 TRs (2.5 s) of rest and a final 144 TRs of rest. The MID task consisted of 96 trials, each lasting 5.8 s (3 x 2.5 s TRs) presented in a pseudorandom order organized into two separate blocks: first a 50% (+$0, 50% ± $1) block of 48 trials, and then a 50% ± $5 block trials. Trial types within blocks were represented in a pseudorandom order. Each trial began with 2 s of cue presentation: either a circle or square, signifying gain or loss, respectively, with a line positioned within the shape horizontally to correspond to the value of the gain or loss (i.e., ±0 trials show a reward in the lower part of the circle/square, and ±1 showing a line in the middle of the shape, and ±5 trials showing a line in the upper part of the shape). Within each trial, each cue period was followed by 1.5–2.5 s of anticipation in which the subject viewed centrally placed fixation cross (+), and a ~0.4-s response period in which the subject had to press a button after the appearance of a white target square within a variably short period (~350 ms, calibrated throughout the task to each subject’s performance) to gain (reward) or avoid losing money (punishment). The subject then received outcome information (2 s) informing him whether he had gained or lost money and the cumulative total. fMRI volume acquisitions were time-locked to the offset of each cue, and voxelwise time courses were then z-scored within each block.

Analyses included both whole-brain and volume of interest (VOI) approaches. For whole-brain analysis, preprocessed time series data for each block were analyzed with a multiple regression model that included four orthogonal regressors of interest: (i) gain (+$5.00 or +$1.00) vs. nongain (+$0.00) anticipation; (ii) loss (−$5.00 or −$1.00) vs. nonloss (−$0.00) anticipation; (iii) “hit” (+$5.00 or +$1.00) vs. “miss” (+$0.00) gain outcomes (iv); and hit (−$0.00) vs. miss (−$5.00 or −$1.00) loss outcomes. Other covariates included two orthogonal regressors highlighting the periods of interest (i.e., anticipation and outcome), six regressors describing residual motion, and six regressors modeling baseline, linear, and quadratic trends for each of two task runs. The regressors of interest contrasted activity during predicted periods (2.5 s each) and were convolved with a single gamma-variate function that modeled a prototypical hemodynamic response (10). Maps of t statistics representing each of the regressors of interest were transformed into Z scores, and spatially normalized by warping to Talairach space.

For VOI analysis, two sets of voxels were chosen for analysis. In the first, an 8-mm sphere centered at the approximate site of implantation in the posterior NAc was created. Second, four voxels within the posterior anatomical boundary of the NAc were selected based on their proximity to the expected site of implantation, as well as their significance in whole-brain analyses (Z > 2.5, P < 0.005, cluster = 4; uncorrected). While data from the second VOI is not independent from whole-brain analyses, it could be independently compared with distinctly acquired LFP recordings. For percent signal change time course plots, signal was extracted from the second VOI, averaged by condition within subject, and plotted for visualization, and paired t test was applied to examine changes in BOLD signal of different anticipations (11).

**Structural MRI (7 T).** To optimize localization of the dorsal boundaries of the NAc in this patient, a 7-T MRI scan was obtained preoperatively using a magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence capable of achieving 1-mm isotropic spatial resolution with whole-brain coverage in ~5 min. This scan was performed on a GE Discovery MR750 7-T scanner (GE Healthcare) with a 2-channel transmit, 32-channel receive head coil (Nova Medical). We first acquired with a three-plane localizer and a higher-order shimming protocol, and then acquired a gray-matter-nulled (GMn) MP-RAGE volume, consisting of a single 3D coronal slab covering the whole brain. Scan parameters for the GMn MP-RAGE sequence were as follows: 224 × 224 matrix; 18-cm field of view; 0.8-mm slice thickness; 280 slices; repetition time, 8.1 s; echo time, 3.7 ms; inversion time, 900 ms; saturation time, 3,700-ms bandwidth, ±21 kHz; ARC parallel imaging factor, 2 × 1; k-space ordering 2D radial fan beam; scan time, 6.66 min. Specific absorption rate (SAR) was monitored in all cases using the vendor-supplied SAR monitor on the scanner and was below 0.5 W/kg for all scans. Using the GMn MP-RAGE image volume, the signal profile along an oblique line passing through the anterior arm of the internal capsule (where the GM fibers are embedded between the GM of the lenticular nucleus on one side and the caudate nucleus on the other side) was plotted. The scan was registered using Framelink software (Medtronic) to a postoperative CT to confirm localization of the implantation site.

**Neural signal recording and analyses.** The DBS lead was then implanted in the NAc using frameless stereotactic techniques, and microelectrode recording determined the dorsal and ventral borders of the left NAc (12). A DBS lead (model 3389; Medtronic) was placed along the single MER track, and the base of electrode 0 was placed at the ventral border of the NAc (along the same trajectory and depth as our permanently implanted 3,391 lead) within the NAc from where these recordings were performed. The more dorsal contacts were above anterior commissure in the anterior limb of the internal capsule and above. We utilized the following entry anterior–posterior commissure coordinates: x = 41.31, y = 43.39, z = 43.59; 34.2° from midsagittal plane; 60.3° from axial plane; and coordinates for the ventral-most extent of the lead: x = 6.03, y = 15.07, z = −6.60. Accumbens was entered 7.3 mm above target. LFPs were recorded differentially from adjacent DBS lead electrode pairs 0–1, 1–2, and 2–3. Limb and head movements were monitored using angular velocity sensors on the limbs (Motus Bioengineering), an accelerometer placed on the forehead, continuous synchronized full-body videography, and intraoperative notes. The participant was instructed to lie still without speaking while keeping his eyes open; the neurologist and psychiatrist (H.B.-S., N.R.W.) monitored him continuously. After 60 s of baseline recording without stimulation, the patient performed the MID task on a laptop.

**Spike–field coupling methodology.** An illustration of how spikes were isolated and removed from the voltage trace to obtain a spike raster and spike-removed LFP is provided. (Note that this...
Voltage measurements. A microelectrode was passed to the ventral NAc using stereotactic guidance. Raw voltage, \( V_0(t) \), was measured by a penetrating microelectrode (0.5- to 1-MΩ platinum–iridium; FHC), reference to the cannula, and acquired by Guideline 3000 microelectrode recording system (Axon Instruments) (gain, 10,000; high-pass filter, 1 Hz; low-pass filter, 10 kHz), passed through a CyberAmp 380 amplifier/filter (Axon Instruments) (gain; 1; high-pass filter, 1 Hz; low-pass filter, 6 kHz), and sampled at 50,000 samples per s using a data acquisition interface (PowerLab) and Spike software (version 2.7) (Cambridge Electronic Design). Task events were recorded by sending digital pulses to an auxiliary audio trace, which was synchronously recorded alongside the voltage trace by the amplifiers.

Identifying action potentials and removing them from the raw voltage. A number of steps were employed to isolate spikes from the voltage trace. First, the raw voltage trace was high-pass filtered at 300 Hz, \( V_0(t) \rightarrow V(t) \).

A linear threshold was visually fit to the filtered voltage trace to capture brief, extreme, characteristic voltage deflections (“spike times”/“action potentials”).

A brief window of data was obtained surrounding the sample of furthest excursion from each deflection, \( \tau_0 \), from 2 ms before to 5 ms after [e.g., \( \hat{V}(\tau) = \hat{V}(t - \tau_0) \)], where \(-2 \text{ ms} \leq t' \leq 5 \text{ ms}\). The average of these windows was the average spike shape. These data windows were then decomposed with a principal-component approach (note that the baseline was, in effect, subtracted off of each window as a byproduct of the high-pass filtering). A singular value decomposition was used to determine the eigenvalues \( \lambda_k \) and eigenvectors \( e_i \) of the correlation matrix \( C(t', t') = \sum V(q) V(q,t') \). These eigenvectors, \( C_k = \lambda_k e_k \), revealed characteristic shapes in the temporal shape of the spike that vary orthogonally, and were ordered by magnitude of corresponding eigenvalue: \( \lambda_1 > \lambda_2 > \cdots \).** Where \( T \equiv \text{number of time points in} -2 \text{ m} \text{s} \text{ to} 5 \text{ m} \text{s} \text{ interval} \). If we defined the rotation matrix \( A(t) = e_1 e_2 \cdots e_7 \), then the projection, \( W(k,q) \), of each individual spike in the ensemble into the new eigenvector space was as follows:

\[
W(k,q) = \sum A(i,k) V(q, t').
\]

The inverse rotation matrix \( A^{-1} \) (where \( A^{-1} A = I \)) allowed us to remove the weighted spike components (the first three eigenvectors) surrounding spike at time \( \tau_0 \) from the raw voltage time series, leaving the LFP:

\[
V(t + \tau_0) = V_0(t + \tau_0) - \sum_{k=1,2,3} A^{-1}(t', k) W(k,q).
\]

Note that the first three eigenvectors should be confirmed to trend to go to zero at \(-2 \text{ ms} \text{ and} 5 \text{ ms} \text{, so that they can be subtracted sensibly without introducing discontinuities in the data}.

Wavelet approach to examine low-frequency oscillatory information at each hertz: A Morlet wavelet of the form: \( \psi(t) = e^{2 \pi f_0 t} e^{-t^2/2} \) was convolved with the LFP timeseries to get a time–frequency estimate for every frequency, \( f \):

\[
\hat{V}(f, t) = \frac{7/2}{\pi} \sum_{l=1}^{7/2} V(l+t') \psi(l+t, f).
\]

A total of seven cycles \((7/2)\) was used to estimate the amplitude and phase of the signal at each frequency for every point in time. In this way, a time-varying Fourier component \( \hat{V}(f, t) = r(f, t) e^{i \phi(f, t)} \), with fixed uncertainty between the confidence in the estimate of the instantaneous amplitude and phase vs. the confidence in temporal resolution was obtained at each hertz.

For each frequency, the coupling between rhythm phase, \( \phi(f, t) \), and individual spike time, \( \tau_0 \), was initially estimated by calculating the number of spikes as a function of the rhythm phase \( \phi \) in small phase intervals. This can be plotted as a two-dimensional histogram palette (spike-field coupling palette in Fig. S5E).

Hilbert transform approach to capture brain rhythms spanning a frequency range band: a complex signal to reflect the time course of a functionally relevant frequency-range band was constructed as follows: the LFP \( \hat{V}(t) \) was bandpassed using a third-order Butterworth filter for a specific range, to obtain the “band-limited” potential, \( V(F, t) \), where \( F \) denotes the frequency range (in our case, \( F = 2 \text{ to} 3 \text{ Hz} \)). A complex, analytic, signal, \( \hat{V}(F, t) = V(F, t) + i V^H(F, t) \), was constructed using the Hilbert transform (e.g., such that the new signal satisfied the Cauchy–Riemann conditions for analyticity at all times). This signal may also be expressed in polar notation: \( \hat{V}(F, t) = r(F, t) e^{i \phi(F, t)} \). The “analytic amplitude” of the range \( F \) at time \( t \) is \( r(F, t) \) and the “phase” is \( \phi(F, t) \). The interpretation of \( \phi \) is intuitively difficult, but the most concrete understanding in our context is that the rhythm captured by range \( F \) is most positive compared with the surrounding brain at \( \phi = 0 \), and most surface-negative at \( \phi = \pi \) or \( -\pi \) (this interpretation would not be valid for bipolar referenced data). Note that \( \phi \) becomes poorly defined as \( r \to 0 \).

To condense the range of frequencies comprising a given rhythm into one measure, the Hilbert transform was applied (as described above), with 2- to 3-Hz frequency range chosen based upon inspection of the spike coupling palette (Fig. S5E). The data were then broken up into epochs corresponding to task parameters (individual cues within each trial).

For each epoch \( E \), a complex-valued “spike–field coupling vector” was calculated by \( Z_{mod} = \sum e_i = 1/N \sum_{s} e_i^s F(t,s) \), where \( NE \) was the total number of spikes in the epoch and \( q = E \) denoted that spike \( q \) occurred during the epoch.

\( Z_{mod} \) was the magnitude of spike–field coupling, intrinsically normalized to 0–1, and \( \phi \) was the preferred coupling phase. To assess the distribution of coupling for \( N \) epochs of a given type, one cannot simply compare the contribution of trial \( n \) to the distribution of coupling values as \( Z_{mod}(n) \) because if \( \phi(n) \) is not reproducible from trial-to-trial, then \( Z_{mod}(n) \) can be a large value even on trials in which the corresponding preferred coupling phase, \( \phi(n) \), is opposite to that of the majority of other trials in the distribution. In other words, the fact that \( Z_{mod}(n) \) must be nonnegative would strongly bias the distribution so that the uncorrected mean of the distribution must be significantly greater than zero even when there would be no underlying coupling of consistent phase.

To account for this, a projected distribution must be obtained, and this was done in the following fashion: first, the global average coupling vector was calculated \( \bar{Z}_{mod} = \sum_{n} Z_{mod}(n) e^{i \phi(n)} \). Note that \( \bar{Z}_{mod} \neq Z_{mod}(n) \mod \bar{\phi}(n) \). Second, the individual epoch coupling vectors were projected onto the phase of the average coupling vector to obtain corrected modulation values, \( Z_{mod}(n) = Z_{mod}(n) \cos(\phi(n) - \phi) \).

The quantities \( Z_{mod}(n) \) can be negative or positive and can therefore have a distribution significantly overlapping with zero (indicating an absence of reliable spike–field coupling). Furthermore, distributions of different types of epochs, each with their own preferred average phase of coupling \( \phi \), can be compared vs. one another or vs. zero (as in Fig. S5G).

Data acquisition and analysis. Principles for electrophysiological data acquisition and analysis in human have been reported previously (5, 13). LFP signals were preamplified with a gain of...
16 by an isolated amplifier (BioAmp 100; Axon Instruments) and then passed through an Axon Cyberamp amplifier/filters providing a total gain of 50,000 with high-pass filtering at 0.5 Hz and low-pass filtering at 400 Hz (14). The kinematic signals (from the accelerometer and angular velocity sensors, all sampled at 1 kHz) and the video recording (30 frames/s) were acquired concurrently with the LFP signals (sampled at 4 kHz) using a data acquisition interface (Power1401) and Spike software (version 2.7) (Cambridge Electronic Design). Signal analysis was performed in MATLAB (version 8.2; The Mathworks). Spectrograms of LFP epochs were generated using a short-time Fourier transform of a 1-s sliding window and 90% overlap, averaged across individual trials based on reward or punishment conditions, and normalized to baselines. The power spectral density estimate was calculated using Welch’s method (1-s sliding window, 50% overlap), averaged across individual trials (2-s epoch starting from cue onset) based on reward or punishment conditions (15).

Fig. S3. (A) Recordings of head movement during MID task in fMRI study (less than 1.5 mm over 15 min). (B) Representative LFP power spectrogram (Top) and head movement (Middle; measured in acceleration (volts)) and limb movement accelerometer traces (Bottom; measured in angular velocity (degrees/second)) during intraoperative MID task. Very little movement was detected except in right limb when the test subject pressed a button (black arrow).
Fig. S4. Normalized delta power in the human NAc during anticipation of high monetary reward was significantly higher than during anticipation of low punishment in the MID task (ANOVA: \( F = 3.964, \ P = 0.0138 \); post hoc pairwise: high reward vs. low punishment: \( P = 0.0070 \)). HP, high punishment; HR, high reward; LP, low punishment; LR, low reward.
Fig. S5. Spike–field coupling in the ventral NAc. (A) Microelectrode recording site. (B) Average spike. (C) First three eigenvectors of principal-component analysis decomposition. (D) First 10 eigenvalues (colors of top 3 corresponding to eigenvectors in C), and projection weights of first 2 eigenvalues, without obvious clustering of more than one spike, suggesting that spikes correspond to a single neuron (Inset). (E) Spike–field coupling palette—mean spike rate (indicated by color) as a function of frequency and phase of Morlet-wavelet derived instantaneous Fourier phase. Note the selective phase-locking of spikes to the peak (phase 0) of the 2- to 3-Hz signal. (F) For each task block, a vector indicated the spike–field coupling (with preferred phase revealed by the angle in the complex plane) is calculated and indicated with a dot (green dots indicate fixation blocks, and blue dots indicate intertrial interval blocks). This gives an idea of the single-trial spike–field coupling, and also the preferred phase of coupling. If there is no significant coupling (e.g., nonzero and reproducible preferred phase of coupling), dot clouds would be symmetrically distributed about the origin. (G) For fixation blocks at each valence, each complex-valued vector in F is projected into the average phase of coupling. This produces distributions of coupling, with means and error bars (SEM) to indicate significance vs. each other and vs. zero. It appears that there is a suppression of spike–field coupling with increasing absolute reward valence (whether positive or negative). The finding of spike–field coupling modulation by valence does establish the saliency of the delta range power as a marker of local computation. Note that the DBS electrode scale field potential recordings of power change during the reward task are not related in any simple way to the spike field and not unexpectedly different from the smaller-scale LFP measured by the microelectrode in this figure. BL, baseline; HP, high punishment; HR, high reward; LP, low punishment; LR, low reward.
Movie S1. Delta-band activity in the NAc was detected immediately before HF intake in mice.

Movie S2. RNS triggered by delta-band activity successfully suppressed binge-like eating behavior in mice. Dashed red line in the power spectrum represented the power threshold to trigger RNS.