Subthalamic low-frequency oscillations predict vulnerability to cocaine addiction

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Identifying vulnerable individuals before they transition to a compulsive pattern of drug seeking and taking is a key challenge in addiction to develop efficient prevention strategies. Oscillatory activity within the subthalamic nucleus (STN) has been associated with compulsive-related disorders. To study compulsive cocaine-seeking behavior, a core component of drug addiction, we have used a rat model in which cocaine seeking despite a foot-shock contingency only emerges in some vulnerable individuals having escalated their cocaine intake. We show that abnormal oscillatory activity within the alpha/theta and low-beta bands during the escalation of cocaine intake phase predicts the subsequent emergence of compulsive-like seeking behavior. In fact, mimicking STN pathological activity in noncompulsive rats during cocaine escalation turns them into compulsive ones. We also find that 30 Hz, but not 130 Hz, STN deep brain stimulation (DBS) reduces pathological cocaine seeking in compulsive individuals. Our results identify an early electrical signature of future compulsive-like cocaine-seeking behavior and further advocates the use of frequency-dependent STN DBS for the treatment of addiction.

addiction | electrical biomarker | compulsive seeking | subthalamic nucleus | deep brain stimulation

Among drug users, only a small fraction of individuals (15 to 20%) transition from recreational use to addiction, through loss of control over their drug intake and compulsive drug seeking despite negative consequences (1). Yet, identifying and anticipating these vulnerable users remains a challenge for both the prevention and the treatment of addictive disorders. In rodents, perseverance of drug seeking behaviors despite negative consequences can be observed by associating a punishment (i.e., mild electric foot shock) with seeking responses. After extended access history to a drug, only 20 to 30% of individuals develop compulsive-like drug seeking, thus capturing individual differences in possible vulnerability to addiction (2–7). This offers a relevant model to study one of the core features of drug addiction in humans (8, 9), which enables critical advances in characterizing brain cellular and molecular alterations following extended cocaine access and exposure to punishment paradigms, notably in neuronal activity and neuroplasticity (2, 10–13). However, addiction research has failed so far to identify alterations in brain regions' activity preceding the behavioral expression of compulsive-like seeking behaviors, especially in the case of cocaine. Such neuronal biomarkers of pathological activity would be of critical importance in identifying subjects susceptible to developing more harmful patterns of consumption and in helping abstinent cocaine addicts before they eventually relapse.

The subthalamic nucleus (STN) displays neurophysiological signatures, especially in terms of abnormal neural oscillations, in Parkinson's disease (PD) (14, 15) and obsessive-compulsive disorder (OCD) patients (16, 17), with a specific oscillatory activity related to compulsive behaviors. Notably, PD patients suffering from impulse control disorders exhibit an increased STN alpha/theta (6 to 13 Hz) activity in response to dopaminergic agonist treatment (18). In healthy human and rat subjects, the STN has been shown to be a key agent in inhibitory control (19, 20). In the context of addiction, the STN has recently received much attention since the demonstration that its lesion or manipulation of its activity with high frequency (130 Hz) deep brain stimulation (DBS) decreases the rat's motivation to work for cocaine, heroin, or alcohol (21–23). Extended access to cocaine during an escalation procedure induces a progressive increase in STN low-frequency oscillations, measured with local field potentials (LFPs), compared to its activity during short access sessions (24). Normalizing these pathological activities with 130 Hz DBS or lesion prevents the escalation of cocaine or alcohol intake and further reduces cocaine, alcohol, and heroin re-escalation normally observed after a period of protracted abstinence (22, 24, 25). STN's contribution to the vulnerability to compulsive seeking of the drug assessed by resistance to a punishment has not yet been investigated. As compulsive-like seeking behaviors typically emerge following extended access to a substance (2, 3, 6, 7, 26, 27), we posit that oscillatory activity within the STN during escalation contributes to the subsequent emergence of compulsive-like cocaine seeking.

Results

Compulsive-like Cocaine Seeking Emerges Only after Loss of Control over Cocaine Intake. Following the acquisition of the seeking–taking task (2 to 3 mo), a control group ($n = 9$) was immediately subjected to eight punished sessions. All animals quickly ceased seeking cocaine when exposed to the punishment contingency (*SI Appendix*, Fig. S1*A*: sessions: $F_{12,\ 96} = 90.66$, $P < 0.0001$).

Significance

Understanding why some individuals become addicts while others can maintain recreational use, and how to treat these individuals, remains a challenge. Using a state-of-the-art rat model of compulsive cocaine seeking (resistance to a punishment associated with cocaine seeking), we show here that: first, subthalamic nucleus (STN) oscillatory activity during prior extended access to cocaine serves as a biomarker to predict vulnerable individuals that will compulsively seek the drug, a hallmark of addiction, and second, that in compulsive "addicted" rats, low (30 Hz) but not high (130 Hz), deep brain stimulation (DBS) of the STN efficiently reduces pathological cocaine seeking. Given that DBS approaches are currently used for neurologic and psychiatric disorders in human patients, our results provide highly translational observations.

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The other animals (n = 53) were subjected to the escalation protocol to lose control over their cocaine intake (*SI Appendix*, Fig. S1*B*: sessions: $F_{14,\ 714} = 6.71$, $P < 0.0001$). Animals were then subjected to five baseline seeking–taking sessions followed by eight sessions with punishment (Fig. 1*A*).

Each animal was retroactively classified on the basis of its seeking performance during the last four punishment sessions. Frequency histogram analysis of the sum of seeking cycles completed revealed a bimodal distribution of individuals, as previously reported (2–5): one "compact" population that completed <10 seeking cycles/4 sessions (n = 36; "shock-sensitive" group) and a "broadly distributed" group that completed ≥12 seeking cycles/4 sessions (n = 17; "shock-resistant" group) (*SI Appendix*, Fig. S1*C*). The distribution of the compulsivity scores of the "shock-resistant" population differs from that of both "shock-sensitive" and control (i.e., those not subjected to the escalation procedure) populations (Kolmogorov–Smirnoff tests D = 1, $P \leq 0.0001$; *SI Appendix*, Fig. S1*C*), while control and "shock-sensitive" groups exhibit comparable distributions (D = 0.3056, not significant [ns]).

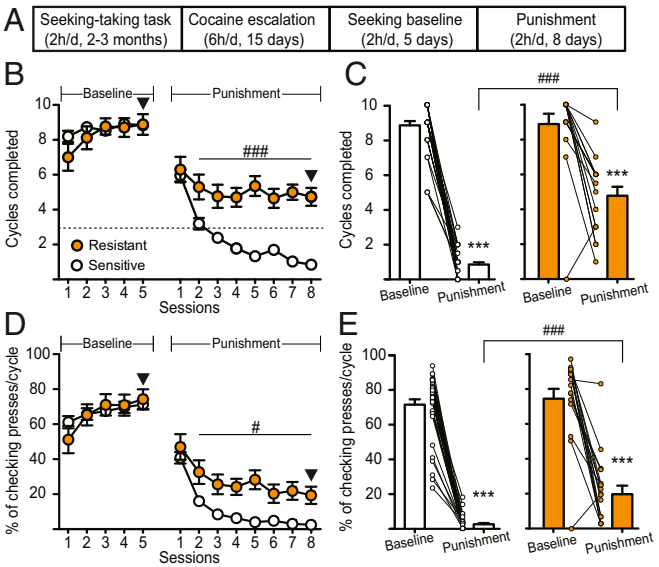

Fig. 1. Escalation of cocaine self-administration promotes compulsive cocaine seeking in a subpopulation of rats. (*A*) The experimental time course. (*B*) Punishment contingency reduced the number of seeking cycles completed in all animals. While both groups displayed equivalent levels of cocaine seeking during baseline, "shock-resistant" rats (i.e., "compulsive," orange dots, n = 17) completed more seeking cycles than "shock-sensitive" rats (white dots, n = 36; Bonferroni post hoc: $^{\#\#\#}P < 0.001$ resistant versus sensitive, 0.89 ≤ Cohen's d (effect size) ≤ 2.44) during punished sessions. The dashed line indicates compulsivity threshold below which animals are considered "shock-sensitive" (*Materials and Methods*). (*C*) The number of seeking cycles completed during the last sessions of baseline and punishment (arrowheads in *B*) for the "shock-sensitive" (*Left*) and the "shock-resistant" (*Right*) groups (Bonferroni post hoc: $^{***}P < 0.001$ baseline versus punishment, 11.89 ≤ Cohen's dz ≤ 12.78; $^{\#\#\#}P < 0.001$ resistant versus sensitive, Cohen's d = 1.44). (*D*) Punishment contingency reduced the percentage of checking lever presses performed per cycle completed. While both groups did not differ during baseline, "shock-resistant" rats (orange dots) performed more checking lever presses than "shock-sensitive" rats (white dots; Bonferroni post hoc: $^{\#}P < 0.05$ resistant versus sensitive, 0.71 ≤ Cohen's d ≤ 1.5) during punished sessions. (*E*) Percentages of checking lever presses performed per cycle completed during the last session of baseline and punishment (arrowheads in *D*) for the "shock-sensitive" (*Left*) and the "shock-resistant" (*Right*) groups; Bonferroni post hoc: $^{***}P < 0.001$ baseline versus punishment, 4.87 ≤ Cohen's dz ≤ 18.53; $^{\#\#}P < 0.01$ resistant versus sensitive, Cohen's d = 1.15). All graphs indicate mean ± SEM. Connected small dots represent individual data points across conditions.

The punishment contingency diminished seeking behavior in all animals (Fig. 1*B*: (sessions: $F_{12,\ 612} = 117.2$, $P < 0.0001$), but "shock-resistant" animals kept seeking cocaine, while the other individuals quickly suppressed this behavior (Fig. 1*B*: sessions × group: $F_{12,\ 612} = 15.85$, $P < 0.0001$; Fig. 1*C*: $F_{1,\ 51} = 35.63$, $P < 0.0001$). They also performed more checking responses than "shock-sensitive" ones (sessions × group: Fig. 1*D*: $F_{12,\ 612} = 4.605$, $P < 0.0001$; Fig. 1*E*: $F_{1,\ 51} = 4.184$, $P < 0.05$), thereby highlighting their recurrent willingness to obtain the drug. In other words, compulsive-like animals cannot refrain their compulsive checking behavior when facing the uncertainty of the seeking's outcome, as observed in a rodent model of OCD (28, 29).

During seeking sessions, animals were given the opportunity to nose poke for an unpunished sucrose reward at any time during the session. Importantly, sucrose seeking was not altered during punished cocaine-seeking sessions in both subpopulations (*SI Appendix*, Fig. S1*D*: session × group: $F_{7,\ 357} = 0.743$, ns), indicating that the effect of punishment was specific to the punished seeking response and did not reflect a general suppression of responding.

Based on behavioral performances, the compulsive nature of each individual only emerged during the punished seeking sessions. Indeed, there was no correlation between the number of training sessions and the future compulsivity score of animals (*SI Appendix*, Fig. S2*A*: r = 0.1479, ns). Seeking performances were equivalent between both populations before cocaine escalation in terms of seeking lever presses, cycles completed, and checking lever presses (*SI Appendix*, Fig. S2 *B–D*: group: 2.278 ≤ $F_{1,\ 51}$ ≤ 2.844, ns). Likewise after escalation, during which both populations displayed similar cocaine intake (*SI Appendix*, Fig. S1*B*: group: $F_{1,\ 51} = 0.448$, ns), both groups exhibited comparable performances during baseline seeking sessions in terms of seeking lever presses (*SI Appendix*, Fig. S2*E*: group: $F_{1,\ 51} = 1.241$, ns), cycles completed (Fig. 1*B*: group: $F_{1,\ 51} = 0.56$, ns), checking lever presses (Fig. 1*D*: group: $F_{1,\ 51} = 0.01$, ns), and sucrose seeking (*SI Appendix*, Fig. S1*D*: group: $F_{1,\ 51} = 0.78$, ns). Finally, there was no correlation between animal's compulsivity score and checking lever presses (*SI Appendix*, Fig. S2*F*: r = 0.06, ns) or seeking lever presses (*SI Appendix*, Fig. S2*G*: r = 0.0911, ns) before exposure to punishment contingency.

STN Low-Frequency Oscillations Predict Compulsive-like Cocaine Seeking. To determine whether changes in STN oscillatory activity induced by escalation of cocaine intake (24) may contribute to the subsequent emergence of compulsive-like seeking, we recorded LFPs through DBS electrodes in n = 17 animals (randomly picked from the n = 53 used for Fig. 1). STN activity was monitored during the 15 min before and after the 6 h session of cocaine intake on days 1, 4, 8, 12, and 15 of the escalation procedure. Following exposure to punishment, animals were classified based on their compulsivity score (n = 12 were "shock-sensitive" and n = 5 were "shock-resistant"). Here again, both populations exhibited comparable levels of cocaine intake during escalation (Fig. 2*A*: group: $F_{1,\ 15} = 0.813$, ns) and basal cocaine seeking (Fig. 2*B*: group: $F_{1,\ 15} = 0.204$, ns).

In contrast, analysis of the LFPs power spectrum revealed two distinct patterns of activity within the STN (*SI Appendix*, Fig. S3 *A* and *B*). Compared to oscillatory activity recorded before the first session of escalation, future "shock-resistant" animals exhibited a progressive increase in STN low (6 to 40 Hz) but not high (65 to 90 Hz) frequency oscillation power during LFPs baseline recordings (i.e., before cocaine access) throughout the escalation procedure, while no changes were observed in future "shock-sensitive" animals (Fig. 2*C*). Although both populations exhibited comparable levels of activity on the first day, band-specific analysis revealed significant power increases in alpha/theta (6 to 13 Hz, Fig. 2*D*: sessions × group: $F_{4,\ 60} = 7.651$, $P < 0.0001$) and beta bands (14 to 40 Hz, Fig. 2*E*: sessions × group: $F_{4,\ 60} = 4.427$, $P = 0.0033$, mostly in the

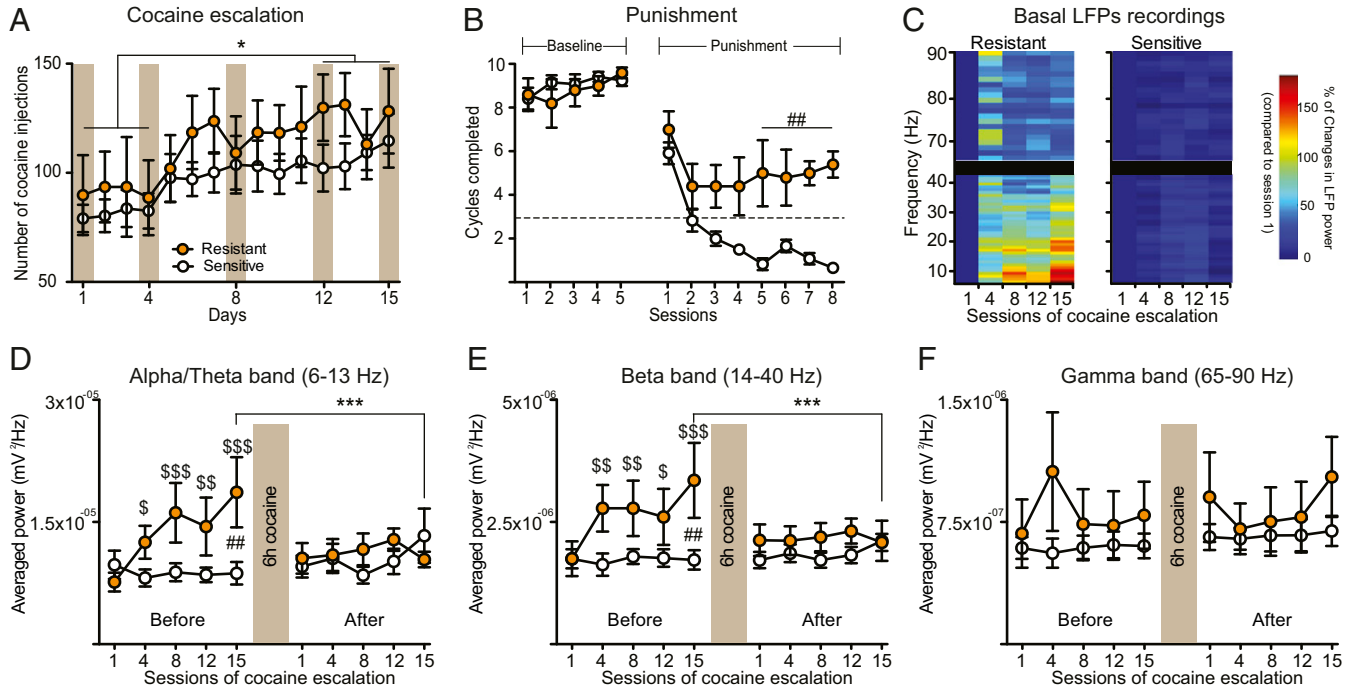

Fig. 2. Compulsive rats exhibit pathological STN low-frequency oscillations during cocaine escalation: a predictive marker for vulnerability to addiction. (*A*) Future "shock-sensitive" (white dots, $n = 12$) and "shock-resistant" (orange dots, $n = 5$) rats exhibited similar drug intake during cocaine escalation (expressed here as the total number of cocaine injections received during each 6 h session; Bonferroni post hoc: $^{*}P < 0.05$, $1.28 \leq$ Cohen's dz (effect size) ≤ 17.28). The brown rectangles indicate LFPs recording sessions. (*B*) "Shock-resistant" rats (orange dots) completed more seeking cycles than "shock-sensitive" rats (white dots; Bonferroni post hoc: $^{\#\#}P < 0.01$ resistant versus sensitive, $0.65 \leq$ Cohen's d ≤ 3.85) during punished sessions. The dashed line indicates compulsivity threshold below which animals are considered "shock-sensitive." (*C*) Session-frequency power spectrum showing basal (i.e., before cocaine) LFPs power changes normalized (in %) to session 1 in "shock-resistant" (*Left*) and "shock-sensitive" (*Right*) animals. (*D–F*) Quantifications of LFPs power before and after 6 h of cocaine access. During baseline recordings (Before), "shock-resistant" rats (orange dots) showed a progressive power increase in alpha/theta and beta (*D* and *E*); Bonferroni post hoc: $^{\$}P < 0.05$, $^{\$\$}P < 0.01$, $^{\$\$\$}P < 0.001$ versus session 1, $1.27 \leq$ Cohen's dz ≤ 3.86) but not in gamma band (*F*). No increase was observed in "shock-sensitive" animals (white dots; Bonferroni post hoc: $^{\#\#}P < 0.01$ resistant versus sensitive, $1.31 \leq$ Cohen's d ≤ 1.5). After the 6 h session of cocaine self-administration (After), the increased baseline power in the resistant animals on session 15 in both alpha/theta and beta bands was reduced (Bonferroni post hoc: $^{***}P < 0.001$, $1.22 \leq$ Cohen's dz ≤ 1.26) but cocaine self-administration had no effect in the gamma band. The line graphs indicate mean ± SEM.

low beta, below 20 Hz as shown in Fig. 2*C* and *SI Appendix*, Fig. S3*D*) only in "shock-resistant" rats. Increased activities were no longer present immediately after cocaine self-administration (sessions × group: Fig. 2*D*: $F_{9,\ 135} = 4.059$, $P = 0.0001$); Fig. 2*E*: $F_{9,\ 135} = 3.514$, $P = 0.0006$).

Importantly, baseline oscillatory activity before the last escalation session was positively correlated with the animal's compulsivity score (*SI Appendix*, Fig. S3*C*) for alpha/theta ($r = 0.605$, $P = 0.01$) and beta bands ($r = 0.513$, $P = 0.035$) but not for the gamma band ($r = 0.187$, ns). Analysis of the change in basal oscillation power of "shock-resistant" rats between the first and the last cocaine escalation sessions indicates that oscillations around 8 Hz were the most dramatically affected at the end of escalation (173.78 ± 49.82% increase, *SI Appendix*, Fig. S3*D*: frequency × sessions: $F_{62,\ 252} = 1.548$, $P = 0.01$). The power of oscillations around 18 Hz were also slightly increased (141.94 ± 59.95% increase).

Causal Contribution of STN Low-Frequency Oscillations to the Onset of Compulsive-like Cocaine Seeking. Next, we sought to confirm the validity of STN alpha/theta pathological activity as a predictive biomarker of compulsive-like seeking behavior. To this end, we first tested whether 8 Hz STN DBS over 6 h (corresponding to the length of an escalation session) could locally increase low-frequency oscillations. Then, we applied this stimulation during an escalation procedure to check whether it promotes compulsive-like seeking in "shock-sensitive" animals by itself (Fig. 3*A*). Pathological oscillations were observed in the absence of cocaine, suggesting that they progressively appear between escalation sessions. Rather than imposing chronic 18 h DBS periods between escalation sessions, we chose to apply 8 Hz DBS during each 6 h escalation session to induce low-frequency oscillation during cocaine intake.

8 Hz STN DBS mimics alpha/theta oscillatory activity. Naïve rats ($n = 4$) with DBS electrodes were daily stimulated at 8 Hz for 6 h for a week. After 6 h of stimulation, STN low-frequency oscillations were markedly increased (*SI Appendix*, Fig. S4*A*: session × frequency: $F_{276,\ 1,112} = 3.461$, $P < 0.0001$), notably in the theta band (6 to 13 Hz) and to a lesser degree in the low-beta band (14 to 18 Hz). No further increase was observed after 7 d of stimulation, indicating that there was no cumulative effect. Band-specific analysis confirmed that 8 Hz DBS increases alpha/theta oscillatory activity within the STN (*SI Appendix*, Fig. S4*B*: $F_{2,\ 8} = 4.465$, $P = 0.05$).

8 Hz STN DBS generates vulnerability to compulsive-like cocaine seeking. We next checked whether 8 Hz STN DBS could induce compulsive drug seeking. Some "shock-sensitive" rats ($n = 13$; Fig. 3*B*: session: $F_{12,\ 120} = 89.94$, $P < 0.0001$), characterized as such after the first escalation–punishment sequence (Fig. 1), were stimulated at 8 Hz ($n = 5$) or 70 Hz ($n = 3$, an oscillatory frequency at which no significant changes were observed in "shock-resistant" rats to serve as control of electrical stimulation, see *SI Appendix*, Fig. S3*D*), during each 6 h session of a second cocaine escalation procedure. Control "shock-sensitive" rats ($n = 5$) remained unstimulated. STN DBS at 8 Hz or 70 Hz had no effect on cocaine intake (Fig. 3*C*: session: $F_{13,\ 130} = 5.302$, $P < 0.0001$; group: $F_{2,\ 10} = 2.142$, ns) and did not change the rats' pattern of cocaine consumption observed during their initial escalation (*SI Appendix*, Fig. S5*A*: session: $F_{14,\ 140} = 3.136$, $P = 0.0003$; group: $F_{2,\ 10} = 0.394$, ns; *SI Appendix*,

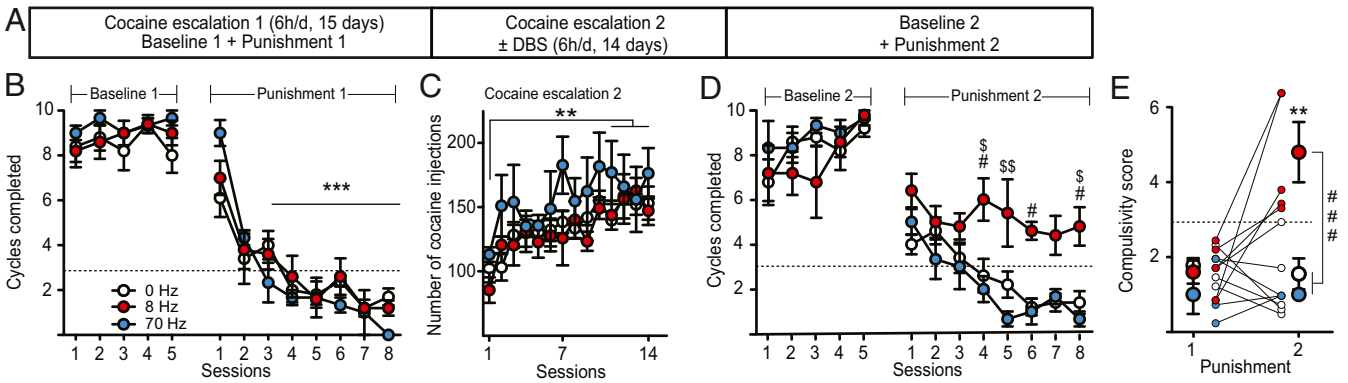

Fig. 3. STN 8 Hz DBS switched "shock-sensitive" rats into "shock resistant" ones. (*A*) The experimental time course. "Shock-sensitive" rats characterized during the initial punishment protocol (Baseline 1 and Punishment 1) were resubjected to a second escalation protocol (escalation 2) before being retested in the punishment protocol (Baseline 2 and Punishment 2). (*B*) Punishment delivery suppressed cocaine seeking in "shock-sensitive" animals (Bonferroni post hoc: $^{***}P < 0.001$, versus baseline 5; $4.73 \leq$ Cohen's dz (effect size) ≤ 20). No stimulation was applied at that stage, but data are illustrated for the various groups to be stimulated at either 0 (white dots), 8 (red dots) or 70 Hz (blue dots). (*C*) STN DBS at 8 Hz (red dots, $n = 5$) or 70 Hz (blue dots, $n = 3$) had no effect on cocaine intake during escalation 2, compared to OFF control group (white dots, $n = 5$; Bonferroni post hoc: $^{**}P < 0.01$, $2.41 \leq$ Cohen's dz ≤ 20). (*D*) Punishment contingency during punishment 2 reduced the number of seeking cycles completed in all groups, but 8 Hz stimulated rats completed more seeking cycles than control and 70 Hz stimulated rats (Bonferroni post hoc: $^{\#}P < 0.05$, 8 Hz versus 0 Hz; $^{\$}P < 0.05$, $^{\$\$}P < 0.01$, 8 Hz versus 70 Hz, $1.78 \leq$ Cohen's d ≤ 3.93) during punishment 2 and reached the criterion to be considered "shock-resistant." (*E*) Compulsivity score before (Punishment 1) and after cocaine escalation 2 (Punishment 2; Bonferroni post hoc: $^{**}P < 0.001$, before versus after, Cohen's dz = 2.9; $^{\#\#\#}P < 0.001$, 8 Hz versus 0 and 70 Hz, $2.27 \leq$ Cohen's dz ≤ 2.9). The dashed lines indicate compulsivity threshold below which animals are considered "shock-sensitive." All graphs indicate mean ± SEM. The connected small dots represent individual data points across conditions.

Fig. S5*B*: session: $F_{13, 140} = 0.601$, ns; group: $F_{2, 10} = 1.079$, ns). This indicates that only 130 Hz STN DBS can reduce re-escalation of drug intake (24). Likewise, the number of cycles completed during the second seeking–taking baseline was similar between groups (Fig. 3*D*: group: $F_{2, 10} = 0.529$, ns) and did not differ from their initial seeking–taking baseline (*SI Appendix*, Fig. S5*C*: session × group: $F_{8, 40} = 1.532$, ns). Levels of checking lever presses during the last session of baseline seeking remained unchanged in all groups (*SI Appendix*, Fig. S5*D*: session × group: $F_{2, 10} = 1.821$, ns).

However, when re-exposed to the foot shock contingency, the 8 Hz stimulated rats displayed a "shock-resistant"–like seeking pattern: they completed more seeking cycles than during the initial punishment phase (*SI Appendix*, Fig. S5*C*: session × group: $F_{14, 70} = 6.687$, $P < 0.0001$), compared to the other animals (controls and 70 Hz) that remained "shock sensitive" (Fig. 3*D*: session × group: $F_{24, 120} = 3.168$, $P < 0.0001$). Accordingly, their compulsivity score was increased (Fig. 3*E*: session × group: $F_{2, 10} = 7.705$, $P = 0.0094$), and they performed more checking lever presses on the last session of punishment (*SI Appendix*, Fig. S5*D*: session: $F_{2, 10} = 6.342$, $P = 0.0305$). Importantly, sucrose seeking level was not altered in any group (*SI Appendix*, Fig. S5*E*: session × group $F_{24, 130} = 0.833$, ns), indicating that 8 Hz STN DBS did not promote a general increase in reward seeking behaviors but a specific increase in cocaine seeking.

Since the STN has been recently implicated in pain processing (30), we also assessed the effect of 8 Hz STN DBS in other animals ($n = 4$) on peripheral pain perception using a hot plate. Neither acute (6 h) nor chronic (6 h/d for 14 d) 8 Hz STN DBS affected animals' latency to react (*SI Appendix*, Fig. S6*A*: $F_{2, 6} = 3.34$, ns), thereby ruling out a possible reduced sensitivity to the aversive effect of shocks in stimulated animals. It is important to note that this hot plate test was performed long after the animals had taken cocaine. Since the punishment by electric foot shock in the seeking–taking task is delivered when the animal is seeking the drug, not when taking it, and after at least 10 min time-out period following the previous cocaine injection, it is thus also received in the absence of cocaine on board (31). This was intended by the design of the task to prevent the stimulant effect of cocaine and its potential local and transient analgesic effect.

STN DBS Reduces Compulsive-like Cocaine Seeking. We next tested the ability of STN DBS to possibly reduce compulsive-like cocaine seeking. Since DBS of the ventral striatum (32, 33) or prefrontal cortex (34) has frequency-dependent effects on drug-induced pathological behaviors, "shock-resistant" ($n = 12$) and "shock-sensitive" animals ($n = 14$) were subjected to both high- (i.e., 130 Hz) and low-frequency DBS (i.e., 30 Hz DBS, a frequency which does not affect premature responses in a serial reaction time task (35) and has no effect on basal or cocaine-induced locomotor activity (*SI Appendix*, Fig. S7 *A* and *B*: DBS: $F_{1, 5} = 0.2445$, ns; cocaine: $F_{1, 5} = 85.67$, $P = 0.0002$.). Animals were stimulated during five punished seeking sessions (i.e., ON; the stimulation lasts for the entire duration of the session) with one DBS frequency (130 or 30 Hz), followed by five punishment sessions with no stimulation (i.e., OFF). They were then subjected to another five ON sessions with the alternate frequency (Fig. 4*A*). Treatment order (130 Hz versus 30 Hz) was counterbalanced.

In contrast to its beneficial effects on other addiction-like behaviors (21, 22, 24), 130 Hz STN DBS temporarily worsened compulsive seeking of "shock-resistant" rats by acutely increasing both the number of cycles completed (Fig. 4*B*: sessions: $F_{14, 336} = 1.764$, $P = 0.043$) and the checking lever presses (*SI Appendix*, Fig. S8*B*: sessions: $F_{14, 336} = 1.718$, $P = 0.05$) during the first two ON sessions. However, this effect was only transient since no significant changes were observed during the last three ON sessions. Accordingly, the global blocks analysis (including the five sessions) revealed no difference between conditions (Fig. 4*C*: $F_{1.711, 18.82} = 1.928$, ns; *SI Appendix*, Fig. S8*C*: $F_{1.688, 18.57} = 1.778$, ns). No changes were observed in "shock-sensitive" rats (Fig. 4*C*: $F_{1.254, 16.3} = 0.7402$, ns; *SI Appendix*, Fig. S8*C*: $F_{1.076, 13.99} = 0.7402$, ns).

During the five 30 Hz ON sessions, "shock-resistant" animals progressively decreased both their number of seeking cycles completed (Fig. 4*D*: sessions: $F_{14, 336} = 3.494$, $P < 0.0001$; Fig. 4*E*: $F_{1.651, 18.17} = 8.095$, $P < 0.01$) and checking lever presses (*SI Appendix*, Fig. S8*D*: sessions: $F_{14, 336} = 2.6$, $P < 0.01$; *SI Appendix*, Fig. S8*E*: $F_{1.145, 12.59} = 5.128$, $P < 0.05$). No changes were observed in "shock-sensitive" rats (Fig. 4*E*: $F_{1.805, 23.47} = 1.058$, ns; *SI Appendix*, Fig. S8*E*: $F_{1.364, 17.74} = 0.273$, ns).

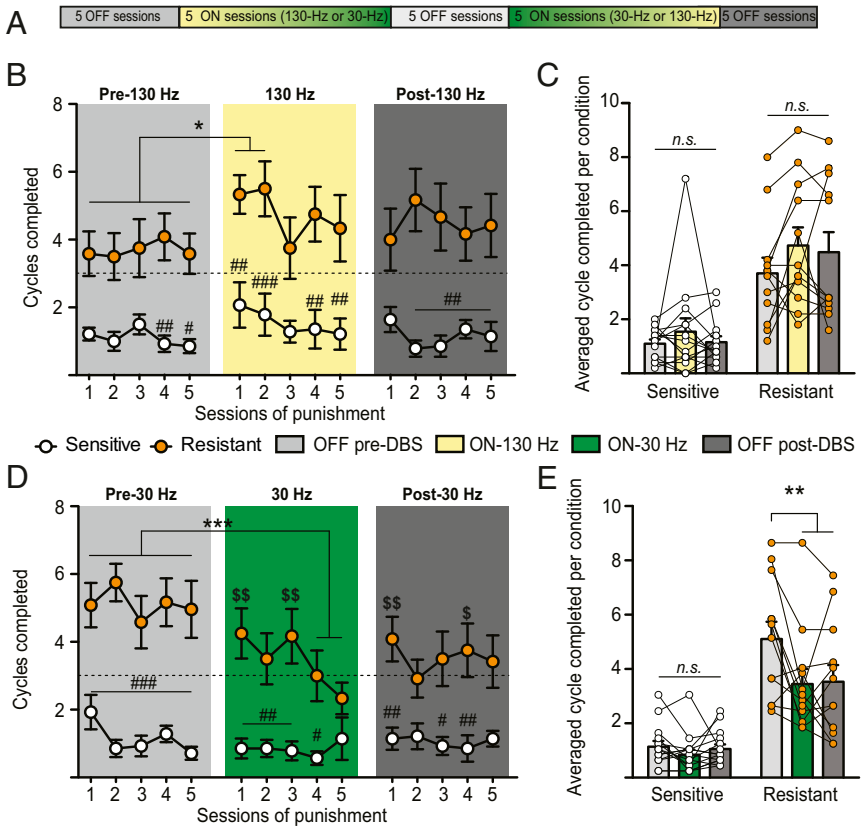

Fig. 4. STN DBS at 30 Hz reduces compulsive-like cocaine seeking. (*A*) The experimental time course: Following five OFF (no DBS) punished sessions, animals were subjected to 5 ON (DBS at 130 or 30 Hz) punished sessions. After five additional OFF sessions, animals were stimulated with the alternate frequency during five ON punished sessions, followed by five OFF sessions. (*B*) STN DBS at 130 Hz (yellow rectangle) acutely increased the number of seeking cycles completed by "shock-resistant" rats during the two first sessions of STN DBS (orange dots; $n = 12$) but had no effect in "shock-sensitive" animals (white dots; $n = 14$; Bonferroni post hoc: $^{*}P < 0.05$ versus Pre-130 Hz, $1.6 \leq$ Cohen's dz (effect size) ≤ 18.29; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$, resistant versus sensitive, $1.16 \leq$ Cohen's d ≤ 1.87). The dashed line indicates compulsivity threshold below which animals are considered shock sensitive. (*C*) Averaged (five-session block) number of cycles completed by "shock-sensitive" (*Left*) and "shock-resistant" (*Right*) rats during punishment sessions before (Pre 130 Hz, pale gray), during (130 Hz, yellow), and after (Post 130 Hz, dark gray) 130 Hz STN DBS. (*D*) STN DBS at 30 Hz (green rectangle) decreased the number of seeking cycles completed by "shock-resistant" rats (orange dots; $n = 12$) but had no effect in "shock-sensitive" animals (white dots; $n = 14$; Bonferroni post hoc: $^{***}P < 0.001$, $2.02 \leq$ Cohen's dz ≤ 18.66; $^{\$}P < 0.05$, $^{\$\$}P < 0.01$ versus last session of 30 Hz DBS, $1.27 \leq$ Cohen's dz ≤ 2.65; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$, resistant versus sensitive, $1.27 \leq$ Cohen's d ≤ 3.24). The dashed line indicates compulsivity threshold below which animals are considered "shock-sensitive." (*E*) Five-session block averaging the number of cycles completed by "shock-sensitive" (*Left*) and "-resistant" (*Right*) rats before (pale gray), during (green), and after (dark gray) 30 Hz STN DBS (Bonferroni post hoc: $^{**}P < 0.01$; $6.45 \leq$ Cohen's dz ≤ 20). All graphs indicate mean ± SEM. The connected small dots represent individual data points across conditions.

Post hoc comparison between ON conditions (five session blocks) highlighted the ability of 30 Hz to reduce "shock-resistant" animals' seeking performance when compared to that achieved under 130 Hz DBS in terms of cycles completed (*SI Appendix*, Fig. S8*F*: $t_{11} = 3.576$, $P < 0.01$) and checking lever presses (*SI Appendix*, Fig. S8*G*: $t_{11} = 2.414$, $P < 0.05$). Also, 30 Hz DBS slightly reduced the number of cycles completed by "shock-sensitive" animals when compared to those completed under 130 Hz DBS sessions (*SI Appendix*, Fig. S8*F*: $t_{13} = 2.268$, $P < 0.05$).

Of note, 30 Hz STN DBS had no noticeable side effects. It did not promote compensatory sucrose seeking in both sensitive and resistant groups (*SI Appendix*, Fig. S9*A*: $F_{5,\ 65} = 0.573$, ns; *SI Appendix*, Fig. S9*B*: $F_{5,\ 55} = 2.099$, ns), and it did not affect animals' latency to react on a hot plate (*SI Appendix*, Fig. S10: sessions × group: $F_{4,\ 12} = 0.2$, ns).

Discussion

Using a rodent model that dissociates "shock-resistant" (compulsive) individuals from "shock-sensitive" ones, we have shown that compulsive-seeking animals exhibit an abnormal low-frequency activity within the STN during extended drug exposure. Causally, applying 8 Hz STN DBS, which locally induces such low-frequency oscillations, during a second escalation turns "shock-sensitive" individuals into "shock-resistant" ones, confirming that abnormal low-frequency oscillations in the STN could serve as a predictive marker for vulnerability to compulsive cocaine seeking. We have also shown that 30 Hz STN DBS reduces compulsive drug seeking, while 130 Hz transiently worsens it, revealing an important frequency-dependent beneficial effect of STN DBS on this criterion of addiction.

Initial behavioral performances could not predict individual compulsive-like phenotypes, which emerged when animals were exposed to the punishment contingency, following extended access to cocaine. STN activity was equivalent in future "shock-resistant" and "shock-sensitive" rats before and after the first extended access to cocaine self-administration but clearly diverged before further sessions of extended access to the drug. Indeed, abnormal alpha/theta and low beta oscillations emerged within the STN of future "shock-resistant" animals only, concomitantly with the progressive increase in cocaine intake. This is in apparent contrast with our former study, in which all recorded animals exhibited a slight increase in baseline STN low-frequency oscillations after 10 d of short access to cocaine (2 h), which was further enhanced during extended access to cocaine (24). These oscillations might have reflected changes in STN activity not only across repeated

extended access to cocaine but also across acquisition of cocaine self-administration. Here, in contrast, LFPs were recorded across cocaine escalation, which occurred after the acquisition of the seeking/taking task, which likely had slightly increased the basal STN low-frequency activities in all animals.

We interpret this neural signature as a predictive electrical biomarker of compulsive-like cocaine-seeking behavior, as no oscillatory changes were observed in future "shock-sensitive" animals. Although these abnormal oscillatory activities appear to be triggered by a drug-dependent process, they are not a direct effect of the drug. In fact, these oscillations were observed during baseline recordings before the daily access to cocaine. During cocaine self-administration, we previously demonstrated that STN low-frequency oscillations remain unchanged during the first 30 min of cocaine escalation sessions (24). In contrast, we show here that increased oscillations were drastically reduced in the immediate aftermath of cocaine extended access sessions, in line with the ability of dopaminergic replacement therapy to reduce PD-abnormal beta oscillations in both PD monkeys and patients (14, 15, 36). However, cocaine has only a transient "masking" effect on these oscillations, as they keep increasing over the course of the escalation protocol (as shown in Fig. 2 *D* and *E*), which likely results from plasticity processes. Also, "artificial" maintenance of alpha/theta activity with STN 8 Hz DBS in "shock-sensitive" animals escalating their cocaine intake is sufficient to subsequently induce compulsive-like seeking when they were re-exposed to the punishment. This clearly establishes the causal predictive nature of STN low-frequency activity to compulsive-like seeking.

The exact origins of these oscillations remain unknown. In contrast to single-unit recordings, accuracy of LFPs recordings is highly influenced by the cytoarchitecture of the recorded region and the origin of the signal (37). Although a contribution of cortical volume-conducted activity cannot be totally ruled out, the bipolar differentials LFPs recorded here, using one electrode wire as an internal reference, may reflect locally generated STN activity (38). The ability of 8 Hz STN DBS to induce local alpha/theta activity in absence of cocaine confirms this hypothesis. Therefore, the pathological increase in STN oscillations observed in "shock-resistant" animals is likely generated nearby the recording site, confirming that STN activity during extended access to cocaine can be used as a readout to predict which individuals having escalated their drug consumption will subsequently develop compulsive-like seeking behaviors.

Several studies have outlined the contribution of STN low-frequency oscillations in motor, emotional, and cognitive processes in PD and OCD patients. For instance, they correlate with levodopa-induced dyskinesia and impulse control disorders in PD patients (18, 39). Also, the severity of compulsive, but not obsessive, symptoms in OCD patients is correlated with STN oscillatory activity within the theta band (16), which is bidirectionally modulated by failure or success to inhibit OCD symptoms (17). Decision making in a high-conflict task has been shown to increase STN theta oscillations (40, 41), which are coordinated with theta activity of the prefrontal cortex during conflict detection (42, 43). Among many other behaviors related to decision-making processes, the prefrontal cortex is involved in reward seeking (44) and directly influences the STN through the hyperdirect pathway (45–47). Prefrontal activity is profoundly affected in human drug users (48), characterized by a loss of top-down executive control, which leads to poor decision making (49). In rats, following extended access to cocaine and exposure to a punished seeking paradigm, prefrontal neurons of "shock-resistant" individuals are more hypoactive than those of "shock-sensitive" ones (2). It is therefore possible that STN pathological low-frequency oscillations during cocaine escalation may propagate throughout the basal ganglia network, as observed in PD (50), to ultimately impose a hypoactive state to prefrontal neurons that would drive afterward compulsive-like seeking in vulnerable individuals. Likewise, in nonvulnerable individuals, 8 Hz STN DBS may thus maintain a pathological hypoactivity in prefrontal neurons during cocaine escalation, possibly through repeated antidromic stimulation of the hyperdirect pathway. Indeed, it has been shown that low-frequency stimulation is more efficient in antidromically and accurately driving cortical neuron activity (51). As such, emergence of STN alpha/theta activity in "shock-resistant" rats (or artificially induced in former "shock-sensitive" animals) during cocaine escalation might thus alter decision-making processes and promote compulsive-like behaviors that would be fully expressed during the exposure to the punishment, when animals have to face the choice to seek drug despite negative consequences.

To date, pharmacological and/or behavioral therapies have failed to produce consistent and long-lasting beneficial effects for humans suffering from cocaine addiction. Our present and previous work has emphasized the therapeutic potential of STN DBS for the treatment of addiction but has also indicated that the frequency used has to be carefully chosen in order to achieve beneficial outcomes and avoid deleterious effects, as described in PD. In rodents and nonhuman primates, low-frequency stimulations drive STN neurons' activity both in vitro and in vivo (52–54), which would then alter STN output structure activities to promote or worsen PD-like motor symptoms in preclinical and clinical studies (55–58). In contrast, high-frequency STN DBS is thought to produce its beneficial effect through inactivation of the STN neurons but also antidromic activation of cortical motor neuron in rodent PD models (51, 58). Likewise, in rodent addiction models, STN DBS appears to differentially affect two different types of compulsive-like behaviors in a frequency-specific manner. While 130 Hz STN DBS efficiently prevents the loss of control over drug intake (22, 24), 30 Hz STN DBS decreases compulsive-like seeking behavior. Mechanisms sustaining these effects remain to be elucidated. Drug-taking and drug-seeking behaviors engage different psychological processes, governed by drug effects and foraging strategies, respectively, which induce imbalances in distinct but overlapping frontostriatal circuits. While both forms of compulsive behavior are consequent to drug-induced dysfunction of cortical areas, such as the prefrontal and orbitofrontal cortices, compulsive taking mostly depends on the dorsomedial and ventral parts of the striatum. In contrast, the loss of prefrontal top-down control over the anterior dorsolateral striatum, which processes drug-seeking habits, drives compulsive seeking (59). Here, 30 Hz STN DBS might antidromically "reboost" hypoactive prefrontal neurons from "shock-resistant" rats to reduce their compulsive-like cocaine seeking, as observed with local prefrontal low-frequency photostimulation (2). However, a possible influence of orthodromic or antidromic activation of STN output or other input structures, respectively, cannot be ruled out. This would affect other pathways involved in compulsive-like behaviors, such as the orbitofrontal cortex to the dorsolateral striatum (60) or the prefrontal cortex to the shell part of the ventral striatum pathways (61, 62). Further studies using circuit- and cell-type manipulation strategies with opto and/or chemogenetics will allow specific dissection of STN-related pathways involved in compulsive-like behaviors.

The fact that 8 Hz STN DBS during escalation of cocaine taking promotes the development of compulsive cocaine seeking in "shock-sensitive" animals while 30 Hz STN DBS promotes punishment-induced suppression of cocaine seeking in "shock-resistant" animals may seem paradoxical. However, in the beta band results shown in the present study, it is mostly the low beta band (below 20 Hz) that seems to parallel the theta modulations. Since 30 Hz belongs to the high beta band, it may thus be involved in different networks and processes. As discussed above, STN theta oscillations and prefrontal-STN theta coupling are known to mediate conflict detection and decision making. In contrast, high beta oscillations are associated with synchronization of the STN with motor cortices and promote motor behavioral inhibition (63, 64). Therefore, it is not surprising that imposing 30 Hz oscillations may facilitate behavioral inhibition of the established cocaine-seeking

behavior in the face of punishment, rendering here the "shock-resistant" animal less compulsive.

The present study identified a predictive electrical biomarker of vulnerability to compulsively seek drug and confirmed the causal role played by STN alpha/theta oscillations during cocaine escalation in the emergence of compulsivity. Such a predictive biomarker, linking pathological intake and seeking, may be of critical importance for developing new diagnostic tools and prevention strategies in humans. Future investigations aiming at detecting cortical correlates of STN abnormal activity, as explored in PD (50), may help to detect in a noninvasive manner (e.g., electroencephalography) vulnerable subjects prone to switch from recreational use to addiction. Also, given the importance of the drug-seeking phase in addiction (59), which offers a potential window for therapeutic intervention to prevent relapse (59), and the successful use of DBS in human neurodegenerative and psychiatric disorders (65, 66), the ability of STN 30 Hz DBS to reduce compulsive-like cocaine-seeking behavior in "shock-resistant" rats, without noticeable side effects, has a highly translational potential. As such, STN DBS–based personalized interventions, in which specific frequencies could be applied at precise stages of drug intoxication, may be of critical importance to efficiently normalize pathological seeking and consummatory behaviors to improve long-term recovery of patients suffering from drug addiction (67).

Materials and Methods

Animals. Adult Lister Hooded males (~380 g, Charles River, $n = 84$) were paired housed, in Plexiglas cages and maintained on an inverted 12 h light/dark cycle (light onset at 7 PM) with food and water available ad libitum, in a temperature- and humidity-controlled environment. At least 1 wk after arrival, animals were subjected to catheter and electrode surgeries (*SI Appendix, Supplementary Methods*). All animal care and use conformed to the French regulation (Decree 2013-118) and were approved by local ethic committee and the Ministère de l'Agriculture (Saisine #3129.01).

Cocaine Seeking–Taking Task. At least 1 wk after surgery, rats began cocaine self-administration training using the seeking–taking chain schedule, as previously described (3). Briefly (see *SI Appendix, Supplementary Methods* for detailed procedures), once rats reached a stable level of cocaine intake (<20% changes across three consecutive sessions) under a fixed ratio schedule (FR-1), they were advanced to the seeking–taking chain schedule. Here, animals had to press a seeking lever to initiate a random interval (RI), which duration was progressively increased throughout training to reach 120 s. Seeking-lever presses within the RI were recorded to establish an index of checking lever presses. The first seeking-lever press following the termination of the RI ends the seeking cycle, materialized by retraction of the seeking-lever and insertion of the taking-lever, in which press triggered the cocaine delivery. Following a 2 min time-out (TO) period (both levers retracted), which duration was progressively increased to 10 min throughout training, a new seeking cycle is initiated. In order to offer them an alternative behavior concurrent to cocaine, rats were also given the opportunity to nose poke into the magazine to obtain 0.04 mL of a 20% sucrose solution, independently to the cocaine seeking–taking schedule, since it was accessible at any time under a 60 s RI. At the end of training, animals were allowed to complete up to 10 cocaine cycles and 120 sucrose deliveries in each 2 h session of the RI120-TO10 schedule.

All animals (except those in *SI Appendix*, Fig. S1*A*) were allowed to escalate their cocaine intake during 15 daily 6 h sessions under a continuous FR1 schedule of reinforcement (68) and then resubjected to five baseline seeking sessions followed by eight punished seeking sessions. Here, half of the completed seeking cycles resulted in mild foot shock delivery (0.5 mA and 0.5 s), with no access to the taking lever. Thus, animals can receive up to five foot shocks and five cocaine infusions during a single session.

Behavioral Index. As in other studies using a similar procedure (2, 3, 7, 26, 27), compulsive-like seeking was quantified by the number of cycles completed, which offers a more accurate index of seeking compared to raw lever presses, given that an individual only has to press the lever twice to end a cycle.

Seeking cycle outcome was pseudorandomly delivered, as the difference between numbers of foot shock and cocaine injection lever cannot exceed 2. With such a design, an individual completing at least three seeking cycles within a single session would inevitably experience both outcomes (e.g., if the two first seeking cycles lead to two consecutive foot shocks, the third cycle will automatically give access to the cocaine-taking lever). Compulsivity score was defined as the average number of completed cycles (foot shock received + cocaine deliveries) during the last four sessions of the punishment paradigm. Animals with a compulsivity score ≥ 3 (i.e., more than 30% of the 10 daily seeking cycles completed) were classified as "compulsive" or "shock-resistant," which represents ~one-third of the population, according to previous reports (2, 3, 6).

Since the end of the highly variable RI (1 to 240 s) was never signaled, animals had to repeatedly monitor or "check" whether they could gain access to the taking lever. To further appreciate the compulsivity of the animals, the percentage of checking lever presses (those unnecessary to complete a cycle performed within the RI) per cycle completed was computed as follows: $100 \times ((\text{checking lever presses/total seeking lever presses}) \times (\text{cycles completed/total cycles}))$ in order to minimize the bias in seeking performance of "shock -sensitive" and "shock-resistant" animals.

Recording and Analysis of STN LFP Activity. LFP recordings were performed in operant chambers equipped with wires connected to the acquisition setup. Animals were connected to the interface and placed in the chamber where they could freely move. STN electric activity was recorded 15 min before and after extended cocaine access on days 1, 4, 8, 12, and 15 of the escalation protocol (Fig. 2*A*).

In another experiment (*SI Appendix*, Fig. S4), LFPs were recorded (15 min) in naïve rats ($n = 4$) before and after the first 6 h session of 8 Hz STN DBS and after seven daily 6 h, 8 Hz DBS sessions.

As previously described (24), signals were amplified and filtered using a Neuralynx8 amplifier. Data were acquired using SciWorks software (Datawave Tech) with a sampling rate of 1 kHz in the range of 1 to 475 Hz. Signals were filtered offline with a Chebyshev low pass filter (corner 98 Hz, order 10, and ripple 0.5), and a notch filter was applied to remove 50 Hz noise created by surrounding electrical devices, using Spike2 software (CED). As such, the analysis was limited to the following frequency bands: 4 to 40 Hz and 65 to 90 Hz. Data were then carefully examined to ensure removal of electrical noise. One wire of the STN bipolar electrode was used as an internal reference to specifically analyze STN activity, calculated as the difference of potentials between the two wires within the same STN. The frequency content of the signal was estimated as the average power spectrum over the whole recording using a sliding window, using Spike2 software (Fast Fourier transformation, Hanning's method, 1,024 points, no overlap). Ultimately, data were treated using Matlab (Mathworks) for visual presentation.

Deep Brain Stimulation. DBS was delivered to the STN by a digital stimulator (DS8000, WPI) via a stimulus isolator (DLS100, WPI) and a rotating commutator (Plastics-One) wired to the implanted electrodes. Stimulation parameters were adapted from previous studies (21, 24). Briefly, individual stimulation intensity was determine using 130 Hz frequency and 80 μs pulse width stimulation. Intensity was progressively increased until the appearance of hyperkinetic movements. Stimulation intensity (50 to 150 μA) was set-up just below the hyperkinetic movement threshold.

Before each behavioral session, animals were connected to the stimulation device, STN DBS was turned ON, and stimulation intensity was progressively increased to reach the predetermined stimulation parameters prior the start of the session. Depending on the condition tested, 8, 30, or 130 Hz were applied during 1, 2, or 6 h, accordingly with the length of the behavioral session.

Statistical Analyses. Data are expressed as mean ± SEM with the exact sample size indicated for each group in figure legends. Using Prism 6.0 (GraphPad) and Matlab (Mathworks) softwares, data were analyzed two-tailed *t* test, one- or two-way repeated measures ANOVAs, followed by Bonferroni post hoc test when applicable. When only one phase of the procedure was relevant to compare between groups, the analysis only included the relevant sessions of the given phase. As for example, if resistant versus sensitive were compared only during the baseline sessions, the punishment phase was not included.

Only P values ≤ 0.05 were considered significant. Effect sizes and power analysis was further performed with the G*Power software to confirm that our sample sizes were sufficient to detect reliable changes for critical experiments (power ≥80%). Effect size values are indicated in the main figure legends and in the *SI Appendix*, Table S1. Power values are indicated in the *SI Appendix*, Table S1.

Data Availability. All study data are included in the article and/or *SI Appendix*.

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