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Midbrain D_3 receptor availability predicts escalation in cocaine self-administration

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Abstract

Background: Results from neuroimaging studies suggest that disruptions in flexible decision-making functions in substance-dependent individuals are a consequence of drug-induced neural adaptations. In addicted populations, however, the causal relationship between biobehavioral phenotypes of susceptibility and addiction consequence are difficult to dissociate. Indeed, evidence from animals suggest that poor decision making due to pre-existing biological factors can independently enhance the risk for developing addiction-like behaviors. Neuroimaging studies in animals provide a unique translational approach for the identification of the neurobiological mechanisms that mediate susceptibility to addiction.

Methods: Here, we used positron emission tomography in rats to quantify regional dopamine $D_{2/3}$ receptors and metabotropic glutamate receptor 5 (mGluR5) and assessed decision making using a probabilistic reversal learning (PRL). Susceptibility to self-administer cocaine was then quantified for 21 days followed by tests of motivation and relapse-like behaviors.

Results: We found that deficits specifically in reward-guided choice behavior on the PRL predicted greater escalation of cocaine self-administration behavior, greater motivation for cocaine, and, critically, was associated with higher midbrain D_3 receptor availability. Additionally, individual differences in midbrain D_3 receptor availability independently predicted the rate of escalation in cocaine-taking behaviors. No differences in mGlu5 receptor availability, responses during tests of extinction or cue-induced reinstatement were observed between the groups.

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Conclusions: These findings indicate that our identified D_3-mediated decision-making phenotype can be used as a behavioral biomarker for the assessment of cocaine use susceptibility in human populations.

Keywords

dopamine D_3 receptor; cocaine self-administration; decision making; reinforcement learning; metabotropic glutamate receptor 5; addiction susceptibility

Introduction

The ability to adapt choices in response to changes in the external or internal environment is disrupted in individuals dependent upon illicit substances (1–3). Studies in animals have found similar decision-making abnormalities in animals chronically exposed to drugs of abuse (4–7) suggesting that the aberrant decision-making processes observed in substance-dependent individuals are, in part, a consequence of drug exposure. However, decision-making problems that are present prior to any drug exposure are also associated with greater drug-taking behaviors (8, 9) suggesting that variability in decision making could be an informative phenotype for elucidating the neurobiology mediating addiction susceptibility.

Reinforcement learning is the process by which action-outcome associations are acquired, stored and updated to guide dynamic decision-making behavior. Theoretically, decisions are guided by action values generated in the brain through multiple computational steps based on previous actions and outcomes. For example, action values might be updated differently depending on whether that action was performed or not and whether the outcome of the chosen action was appetitive or aversive (10). Reinforcement-learning algorithms can quantify the degree to which these individual computational steps influence choice (11–13), and have been used to interrogate the decision-making processes that are affected in drug exposed humans and animals (7, 14, 15). The reinforcement-learning processes that underlie susceptibility to drug use, however, are not known.

We have reported that disruptions in reward-guided choice behavior during decision-making tasks are associated with greater methamphetamine self-administration (8) and that individual variation in reward-guided choice behavior is related to midbrain D_3 receptor availability (16). Midbrain D_3 receptor availability is higher in stimulant-dependent individuals compared to control subjects (17–19) and antagonism of D_3 receptors reduces drug self-administration in rodents (20, 21). High midbrain D_3 receptor availability prior to drug use may, therefore, enhance drug use susceptibility by disrupting reward-mediated decision-making processes.

To investigate this hypothesis and explore the role of metabotropic glutamate receptor 5 (mGluR5) in decision making and addiction susceptibility, we assessed decision making in adult, male rats using a probabilistic reversal learning (PRL) task and quantified *in vivo* dopamine $D_{2/3}$ and mGlu5 receptor availability with positron emission tomography (PET). Rats were then trained to self-administer cocaine or saline in 6 h daily sessions for 21 days. We hypothesized that poor performance of rats in the PRL would be associated with reduced reward-guided choice behavior, higher [^{11}C]-(+)-PHNO binding in the midbrain, where

binding is exclusively due to D_3 receptors (22, 23), and greater cocaine-taking behaviors. Together our study establishes putative links between decision-making performance, dual-tracer PET imaging of dopamine D_3 and mGluR5 availability, and subsequent cocaine-taking behaviors.

Materials and methods

Animals

Adult, male Long Evans rats (N=50) were obtained from Charles River (Raleigh, NC) at approximately 6 weeks of age (Supplement).

Probabilistic reversal learning (PRL) training

Decision making was assessed on a 'three-armed bandit' probabilistic reversal-learning (PRL) task using stochastic reward schedules (Figure 1A; Supplemental Figure 1). On each trial, three noseport apertures were illuminated with one of the apertures being associated with a higher probability of delivering reward than the other two apertures. Reinforcement probabilities assigned to each noseport were pseudo-randomly assigned at the start of each session for individual rats. Rats could make a single choice on each trial by making a noseport entry into the illuminated port. After completing 120 trials (referred to as the Acquisition phase), the probability of reward delivery changed and rats completed 120 additional trials under this new reward schedule (referred to as the Reversal phase).

Decision making in the PRL was assessed using two different schedules of reinforcement: the PRL high probability (referred to as the PRL-HP) schedule had a larger dynamic range than the PRL low probability (referred to as the PRL-LP) schedule (Supplemental Figure 1). Decision making was assessed in six sessions using either the PRL-HP schedule (session 1, 3, and 5) or the PRL-LP schedule (session 2, 4, and 6). Performance of rats in the PRL-HP was strongly correlated with that in the PRL-LP (Supplemental Figure 1), so dependent measures were collapsed across the two schedules of reinforcement.

Outcome-based measures

To characterize the decision-making processes responsible for differences in PRL performance, we examined how previous trial outcomes and choices influenced choice behavior on the current trial. First, we calculated the probability that rats would stay after a rewarded and correct response and the probability that rats would switch their choice after an unrewarded and incorrect response (24). To determine if the differences we observed using this single-trial back analysis extended to more distant trials in the past, choice behavior was then analyzed with a logistic regression that included choices and outcomes from trials in the recent history (t-1 through t-4). This model quantifies the degree to which choices and outcomes (rewarded or unrewarded) on the previous four trials influence current choice behavior (7, 24). Regression coefficients estimate the change in the likelihood of repeating the same choice relative to an arbitrary baseline. Positive regression coefficients indicate that the rats are more likely to persist with the same choice, whereas negative regression coefficients indicate that rats are more likely to shift their choice.

Reinforcement-learning model

The choice behavior of rats in the PRL also was analyzed with a differential forgetting reinforcement-learning model (10, 24, 25), which captures gradually decaying effects of previous choices and outcomes relationships more formally than those captured by the outcome-based measures described above. This model fits the choice behavior of rats significantly better than other reinforcement-learning models (see Supplemental methods and Supplemental Table 1). This reinforcement-learning model, described in detail in the Supplement, contains four free parameters: a decay rate for the action values of chosen options (γ_C), a decay rate for the action values of unchosen options (γ_U), a parameter for the appetitive strength of rewarded outcomes (Δ_+), and a parameter for the aversive strength of unrewarded outcomes (Δ_0).

PET Imaging and Processing

Once rats completed the PRL testing (~6–8 weeks), they underwent PET scans to quantify $D_{2/3}$ receptor and mGluR5 availability using [^{11}C]-(+)-PHNO and [^{18}F]FPEB, respectively, during one serial PET scanning session which was collected ~1 week before starting the cocaine or saline self-administration procedure. The procedures for acquiring and processing the dynamic PET data are described in the Supplement. Activity concentration was extracted from six regions of interest (ROI): the medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), ventral striatum (VS), dorsal striatum (DS), midbrain and cerebellum. These regions were selected based on previous work that has observed differences in [^{11}C]-(+)-PHNO or [^{18}F]FPEB binding in substance-dependent individuals (18, 19, 26, 27). Analyses of [^{11}C]-(+)-PHNO binding were restricted to the VS, DS and midbrain given evidence of negligible specific binding in the prefrontal cortex (28). Time-activity curves from each ROI were fitted with the multilinear reference tissue model (MRTM) using activity from the cerebellum as the reference region (29, 30) to provide estimates of BP_{ND}, R_1 and k_2'. The primary outcome measure for both radiotracers was BP_{ND}, which is directly proportional to the number of receptor sites available for radioligand binding (31).

Self-administration procedures

Rats were implanted with intrajugular catheters as previously described (8) and were trained to self-administer cocaine (0.5 mg/kg/infusion) or saline in 6 h daily sessions for 21 days (Supplement). Rats were trained on a fixed ratio (FR) 1 schedule for three days to establish operant responding. The operant requirement was then changed to a FR3 schedule for the additional 18 self-administration days.

Characterizing latent drug-taking phenotypes

The number of drug infusions each rat earned across the 21 days of self-administration were fitted with a power function, as we have previously described (8):

$$f(x) = Ax^B$$

where x is the session number during the self-administration procedure ($1 \leq \times \leq 21$) and A and B are parameters estimating the scaling factor and rate of growth, respectively. The A

parameter determines the initial strength of the drug-taking behavior and the B parameter determines the rate of growth of the function (Supplemental Figure 3).

Assessing addiction-relevant behaviors

Additional tests of drug-taking and -seeking behaviors were examined following the 21 d self-administration procedure using procedures previously described (32–34). Motivation to obtain an infusion of cocaine or saline was assessed under a progressive ratio schedule and drug-seeking behavior assessed in a cue-induced reinstatement test as described in the Supplement.

Statistical analyses

Statistical analyses are described in the Supplement.

Results

Poor reversal learning is associated with disruptions in reward-mediated updating

Decision making was assessed in adult, male rats (N=50) on a 'three-armed bandit' probabilistic reversal-learning (PRL) task (Figure 1A) using stochastic reward schedules (Supplemental Figure 1). Rats were able to track these dynamic reinforcement probabilities (Figure 1B) and, as expected, chose the most frequently reinforced option significant less following a change in reward probabilities compared to their performance in the acquisition phase (Figure 1C; χ^2=62.05; p<0.001). Performance in the reversal phase, however, was still significantly above chance (t(49)=10.85; p<0.001) demonstrating that rats, on average, were able to adaptively adjust their choices following the change in reinforcement contingencies.

There was, however, a large amount of variation in the performance of rats during the reversal phase of the PRL (Figure 2A) that we hypothesized may be related to susceptibility to drug use. Rats were divided into two groups based on a median split of performance in the reversal phase (Figure 2A) into rats with good reversal performance (referred to as 'good reversal'; N=25; mean: 0.63±0.01; dark blue) and rats with poor reversal performance (referred to as 'poor reversal'; N=25; mean: 0.43±0.02; light blue). The performance of rats in the acquisition phase did not differ between these groups (χ^2=2.70; p=0.10) indicating that rats in the good and poor reversal groups were able to acquire the discrimination to a similar degree. As expected when using a median split design, reversal performance was significantly worse in the poor reversal group compared to the good reversal group (group: χ^2=65.68; p<0.001; Figure 2B-C).

This disparity in reversal performance observed between the good and poor reversal groups could be driven by impairments in select reinforcement-learning mechanisms. The probability that rats would persist with a rewarded and correct response and the probability that rats would switch after an unrewarded and incorrect response was compared between the groups (8). The poor reversal group was significantly less likely to persist with a rewarded and correct choice compared to the good reversal group (χ^2=27.96; p<0.001; Figure 2D). No group differences were observed in the probability that rats would persist

with an unrewarded and incorrect choice (χ^2=0.01; p=0.92) indicating that poor reversal performance was specifically due to deficits in reward-based updating.

To determine whether this impairment extended into the recent history of choices and outcomes (e.g., t-1 to t-4) the regression coefficients for the 'Reward' and 'No reward' predictors in the logistic regression model were examined between the good and poor reversal groups. There was a significant group x outcome x trial interaction (χ^2=10.69; p=0.01; Supplemental Figure 2) and post-hoc analyses indicated that the regression coefficients for the 'Reward' predictor were significantly lower in the poor reversal group compared the good reversal group (group: χ^2=7.32; p=0.007; Figure 2E; Supplemental Figure 2). Consistent with the single-trial back analysis, the regression coefficients for the 'No reward' predictor did not differ between the groups (group × trial: χ^2=0.37; p=0.55).

Reinforcement-learning models predict that choices based on action values are adjusted incrementally according to previous actions and outcomes over multiple trials. Such models might be more sensitive to subtle changes in the effect of previous outcomes on decision-making performance compared to the logistic regression analyses presented above. Choice data during the reversal phase of the PRL was fit with a differential forgetting reinforcement-learning model and parameter estimates compared between the groups. Post-hoc analyses of the group x parameter interaction (χ^2=8.14; p=0.04) indicated that the Δ_+ parameter was significantly lower in rats with poor reversal performance compared to those with good reversal performance (χ^2=6.19; p=0.01; Figure 2F). No other significant group differences were detected (χ^2<1.19; p>0.27). These results, collectively, indicate that the disparity in reversal performance observed between the good and poor reversal groups is due specifically to differences in updating of reward-guided choice behavior.

Poor reversal learning is associated with high midbrain D_3 receptor availability

Reconstructed, three-dimensional [^{11}C]-(+)-PHNO and [^{18}F]FPEB PET images were co-registered to a rat MR template and activity extract from six regions of interest to generate time activity curves (Figure 3A,B). The distribution of [^{11}C]-(+)-PHNO and [^{18}F]FPEB observed in our rats was similar to that previously reported (16, 30) and binding potential maps revealed anatomical differences in non-displaceable binding potential (BP_{ND}) that are consistent with the known distribution of dopamine D_3 receptors and mGluR5 (Figure 3C,D).

We have previously reported that reversal performance is negatively correlated with midbrain D_3 receptors (16). To determine if midbrain D_3 BP_{ND} differed in this sample of rats, [^{11}C]-(+)-PHNO BP_{ND} across the three regions of interest was compared between the good and poor reversal groups. Post-hoc analyses following a significant group x brain region interaction (χ^2=8.75; p=0.01) indicated that midbrain [^{11}C]-(+)-PHNO BP_{ND} was significantly higher in the poor reversal group compared to the good reversal group (group: χ^2=9.45; p=0.002; Figure 3E), thus confirming our previous results. No significant differences were detected for the other brain regions (group: all χ^2<0.07; p>0.79). We then examined whether mGluR5 BP_{ND} differed between the good and poor reversal groups. The group x brain region interaction and the effect of group, however, were not significant (group x brain region: χ^2=3.56; p=0.47; group: χ^2=0.20; p=0.66; Figure 3F).

Poor reversal learning is associated with greater cocaine self-administration

Following the dual-tracer PET imaging, rats were implanted with intrajugular catheters and trained to self-administer cocaine (N=34) or saline (N=8) in 6 h daily sessions for 21 days (Figure 4A). The number of infusions rats earned across the 21 days significantly increased in the cocaine group (χ^2=180; p<0.001), whereas the number of infusions earned decreased in the saline group (χ^2=971; p<0.001; Figure 4B).

Cocaine self-administration was then compared between the good and poor reversal rats. The number of cocaine infusions animals earned in each daily session increased across the 21 days of self-administration but the rate of increase was significantly higher in the poor reversal group (group x day: χ^2=60.63; p<0.001; Figure 4C). Rats in the poor reversal group took significantly more cocaine than rats in the good reversal group across the 21 d of self-administration (χ^2=4.66; p=0.03; Figure 4D). Moreover, this effect was significant when reversal performance was entered as a covariate (day x reversal p(correct): χ^2=37.35; p=0.01) rather than as a discrete factor.

The cocaine self-administration data for individual rats was fit with a power function to estimate the initial reinforcement of cocaine (e.g., A parameter) and the rate of escalation in drug use (e.g., B parameter) as we have previously described (8). The A parameter did not differ between the groups (χ^2=0.84; p=0.36; Figure 4E), but a difference between the groups was observed for the B parameter (χ^2=3.70; p=0.05; Figure 4F): rats in the poor reversal group escalated their cocaine intake at a rate greater than rats in the good reversal group.

We then examined whether there were differences in responding under a progressive ratio (PR) schedule between the good and poor reversal groups. Rats in the poor reversal group reached a higher final ratio on the PR schedule (χ^2=3.37; p=0.06; Figure 4G) and made significantly more active lever responses compared to rats in the good reversal group (χ^2=4.63; p=0.03). However, this heightened response rate was not specific to the cocaine-paired lever as we also observed more inactive lever responses in the poor reversal group compared to the good reversal group (χ^2=5.15; p=0.02). These results indicate that rats in the poor reversal group had a greater level of motivation to obtain a cocaine infusion compared to rats in the good reversal group.

We then examined whether differences in reversal performance prior to drug use were associated with differences in responding under extinction and a reinstatement test. The number of active presses during the extinction test did not differ between the groups (χ^2=0.06; p=0.81; Figure 4H). One rat in the good reversal group was excluded from the analysis of the reinstatement test because the number of active lever responses (e.g., 881) was more than 10 standard deviations from mean. Regardless, responding of rats in the cue-induced reinstatement test did not differ between the good and poor reversal groups (χ^2=0.20; p=0.66; Figure 4I).

Midbrain D_3 BP_{ND} is associated with reward-mediate updating of choices and rate of escalation in drug use

The results presented here indicate that poor reversal learning is associated with reduced reward-mediated updating of behavior, higher midbrain D_3 BP_{ND}, and greater escalation in

cocaine intake. These data suggested to us that midbrain D_3 BP_{ND} may be a mechanistic point of convergence between reward-guided decision making and susceptibility to drug use. To investigate this possibility directly, we examined the relationships between midbrain [^{11}C]-(+)-PHNO BP_{ND}, the Δ_+ parameter and cocaine self-administration parameters. Consistent with our previous findings (16), midbrain [^{11}C]-(+)-PHNO BP_{ND} was negatively related to the Δ_+ parameter (R^2=0.28; p=0.002): as midbrain [^{11}C]-(+)-PHNO BP_{ND} increased across rats, the Δ_+ parameter decreased (Figure 5A). We also observed a negative relationship between the Δ_+ parameter and the B parameter estimate (R^2=0.13; p=0.04; Figure 5B). As expected, midbrain D_3 BP_{ND} was positively related to the B parameter estimate (R^2=0.11; p=0.05; Figure 5C).

To further explore the relationships between midbrain [^{11}C]-(+)-PHNO BP_{ND}, reward-mediated updating and escalation in drug use (e.g., the B parameter), a mediation analysis was conducted using multiple regressions (35). The positive relationship between midbrain [^{11}C]-(+)-PHNO BP_{ND} and the B parameter (R^2=0.11; p=0.05) was attenuated when the Δ_+ parameter was included in the model (R2=0.03; p=0.34). Although the total effect was significant (t=2.28; p=0.03), the indirect effect was not (95% CI: −0.025–0.3826) suggesting that the Δ_+ parameter only partially mediated the relationship between midbrain [^{11}C]-(+)-PHNO BP_{ND} and the B parameter.

Discussion

In the current study, we provide new evidence that heightened midbrain D_3 BP_{ND} is associated with deficits in reward-guided decision making and predicts greater susceptibility to cocaine-taking behavior. Using a dynamic decision-making task and computational approaches, we demonstrate that poor reversal learning performance is associated with impairments in reward-mediated updating of choice behavior, higher midbrain D_3 BP_{ND} and greater escalation in cocaine self-administration. Moreover, we provide direct evidence that relates midbrain D_3 BP_{ND} with reward-mediated updating of choice and escalation in cocaine self-administration, which offers mechanistic insight into the biobehavioral mechanisms of addiction susceptibility. Together, these results indicate that the midbrain D_3 receptor may be a unique biomarker of cocaine use susceptibility.

Disruptions in decision making predict greater susceptibility to drug use

Drug-induced neural adaptations are believed to be the mechanism by which disruptions in adaptive, flexible decision making emerge in substance-dependent individuals. Our data, however, indicate that poor decision-making prior to drug exposure is associated with an enhanced susceptibility to cocaine use. Specifically, we found that rats with poor reversal performance escalated their cocaine intake at a rate significantly greater than rats with good reversal performance. Higher rates of drug use escalation are associated with an increased risk for problematic drug use in humans (36–39) and, therefore, likely to be a meaningful predictor of addiction liability. These findings are consistent with previous work in mice (9) and suggest that the decision-making deficits observed in substance-dependent individuals may, in part, have been present prior to initiation of drug use.

The decision-making deficits observed in the poor reversal group was specific to reward-mediated updating: rats with poor reversal performance were less likely to persist with a rewarded, correct response and had a lower computationally-derived Δ_+ parameter. Moreover, individual differences in the Δ_+ parameter were negatively related to the rate of escalation in cocaine use, which was consistent with our previous findings (8). This work, collectively, suggests that individual differences in reward-guided choice behavior could serve a non-invasive behavioral phenotype for assessing psychostimulant susceptibility in humans. Indeed, a recent study in occasional recreational stimulant users reported that reward-mediated choice behavior in a Risky Gains Task predicted risk for future stimulant use disorder (40).

The precise decision-making factors that confer risk for cocaine use may differ from those decision-making processes that are disrupted by persistent drug use. Emerging evidence indicates that choice behavior following negative feedback is selectively disrupted in substance-dependent individuals (41–43), as well as in animals following psychostimulant self-administration (7, 8, 15). We propose, based on the current data, that individual differences in action-value updating that follows positive feedback mediates the initial stages of drug use by regulation of drug intake over time. In contrast, drug-induced changes in action-value updating that follows negative feedback may contribute to the development of compulsive drug-taking behaviors that emerge after extended drug use. We plan to test this hypothesis by examining the relationship between compulsive drug-taking behaviors and drug-induced changes in negative feedback updating measured by the PRL task. These select reinforcement-learning mechanisms are controlled by anatomically distinct orbitofrontal circuits (24) that may provide critical insights into the neural circuits underlying addiction.

Dopamine D_3 receptors and susceptibility to drug use

We hypothesized that high D_3 receptor density would increase drug use susceptibility by disrupting flexible, adaptive decision making (16). Here, we provide direct evidence supporting this hypothesis. Rats with poor reversal performance had greater midbrain D_3 BP_{ND} and a higher rate of escalation in cocaine intake compared to those rats with good reversal performance. Our findings suggest that high midbrain D_3 BP_{ND} that has been observed in stimulant-dependent populations (17–19) may have been present prior to drug use and contributed to the development of addiction. D_3 selective antagonists reduce drug self-administration (21, 44, 45), conditioned place preference (20, 46) and relapse-like behaviors in rodent models (20, 47, 48) that also argues for a critical role of the D_3 receptor in addiction-relevant behaviors. The mechanism by which midbrain D_3 BP_{ND} impacts prefrontal-mediated, decision-making processes is unknown, but there is evidence that greater midbrain D_3 receptor availability is associated with reduced functional connectivity between the orbitofrontal cortex and cognitive control networks (49). Midbrain D_3 receptors act as autoreceptors and regulate the release of dopamine in striatal regions (50). Individuals with higher midbrain D_3 receptor availability may have reduced dopamine tone in key dopaminergic circuits that regulate decision making (51). Blunted dopamine transmission has been hypothesized to mediate addiction liability (52), but there is evidence that amphetamine-induced dopamine release in the striatum is positively related to self-report measures of impulsivity (53), a known predictor of addiction. Studies that combine

temporally discrete measures of dopamine dynamics with PET neuroimaging and drug self-administration in animals could provide critical insights into the role of midbrain D_3 receptors and cocaine use susceptibility.

The lack of group differences in striatal [^{11}C]-(+)-PHNO binding was surprising based on our previous work (54, 55). We did, however, observe a non-significant *negative* relationship between [^{11}C]-(+)-PHNO binding in the dorsal striatum – where binding is almost exclusively reflective of D_2 receptors (22, 23) – and the rate of escalation in cocaine intake ($R = -0.26$; $p=0.13$; Supplemental Figure 4). Future [^{11}C]-(+)-PHNO PET studies that use D_2 selective antagonist to isolate the D_3 receptor signaling could help determine the role that D_3 receptors in other brain regions play in addiction-relevant behaviors.

We found that the decision-making processes that enhance susceptibility to cocaine use was specifically associated with greater midbrain D_3 receptor availability, as mGluR5 BP_{ND} did not differ between the good and poor reversal groups. The lack of differences in mGluR5 BP_{ND} was somewhat surprising as pharmacological manipulations of mGluR5 signaling alter reversal learning (56) and spatial learning (57), as well as reducing drug self-administration (58, 59). Previous PET studies have reported that mGluR5 BP_{ND} is lower in cocaine-dependent individuals (26, 27) and decreases in rats following cocaine self-administration (60). Disruptions in mGluR5 signaling, therefore, could be the mechanism contributing to cocaine-induced decision-making deficits.

In summary, this study demonstrates that D_3-mediated disruptions in reward-guided choice behavior predict susceptibility to cocaine use in rats. These results integrate human-based neuroimaging and computational approaches with measures of addiction-relevant behaviors in rats. This adds to a growing body of work indicating that D_3 receptor dysregulation contributes to the behavioral mechanisms underlying addiction susceptibility and provides a rationale for translational investigations into vulnerable populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SMG and JRT were responsible for the conceptualization. SMG, KF, and DH were responsible for investigation. AH and HL were responsible for software. SMG was responsible for analysis and writing the original draft. SMG, AH, HL, KF, DH, EM, DL, and JRT were responsible for writing, reviewing and editing. All authors approved the final version of the manuscript.

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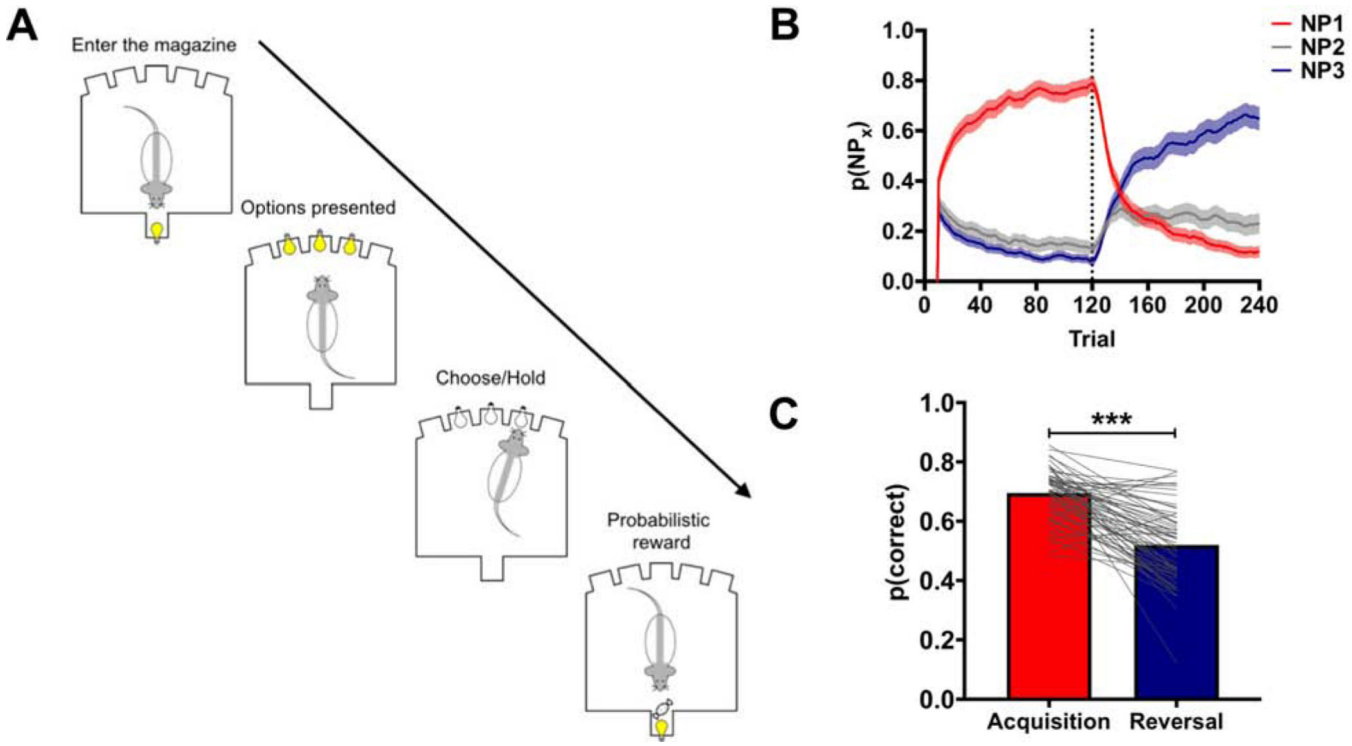

Figure 1:

The probabilistic reversal learning (PRL) task. (A) A diagram outlining the events of a single trial in the PRL task. (B) The choice behavior of rats in the PRL. Rats were able to acquire (red line) and reverse (blue line) their choices in the PRL using a 10-trial moving average. The gray line is the probability of rats choosing the noseport associated with an intermediate probability of reinforcement. (C) The probability of choosing the highest reinforced option was significantly lower following the reversal. *** $p<0.001$. Related to Supplemental Figure 1.

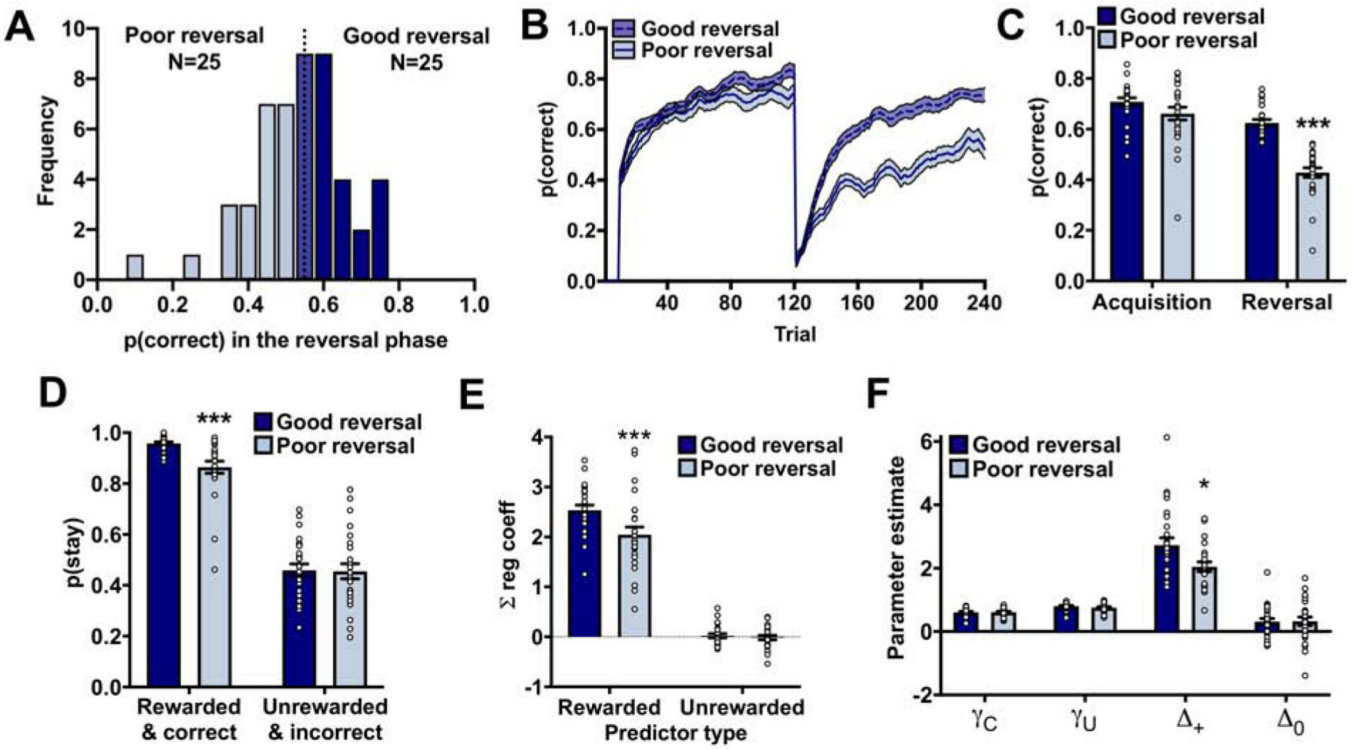

Figure 2:

Differences in reversal performance are due to differences in action-value updating following positive feedback. (A) Frequency distribution of the performance of rats in the reversal phase. Rats were divided into two groups based on a mean-split: rats who chose the correct noseport with a probability greater than the group average (good reversal; dark bars; N=25) and rats who chose the correct noseport with a probability less than the group average (poor reversal; light bars; N=25). (B) The choice behavior of rats in the good and poor reversal group in the PRL using a 10-trial moving average. (C) Rats in the poor reversal group were able to acquire the initial discrimination, but had greater difficult following the reversal. (D) The poor reversal group were less likely to stay with a rewarded and correct response compared to the good reversal group. No group differences were observed in the probability that rats would stay with an unrewarded and incorrect response. (E) The logistic regression model containing a 'Reward' and 'No reward' predictor indicated that the poor reversal group were less likely to use positive feedback from recent trial history to guide their current choice compared to the good reversal group. No group differences were detected for the 'No reward' regression coefficients. (F) The reinforcement-learning algorithm indicated that the poor reversal group had a selective reduction in the Δ_+, as no differences were detected in the other parameter estimates. * $p<0.05$; *** $p<0.001$. Related to Supplemental Figure 2.

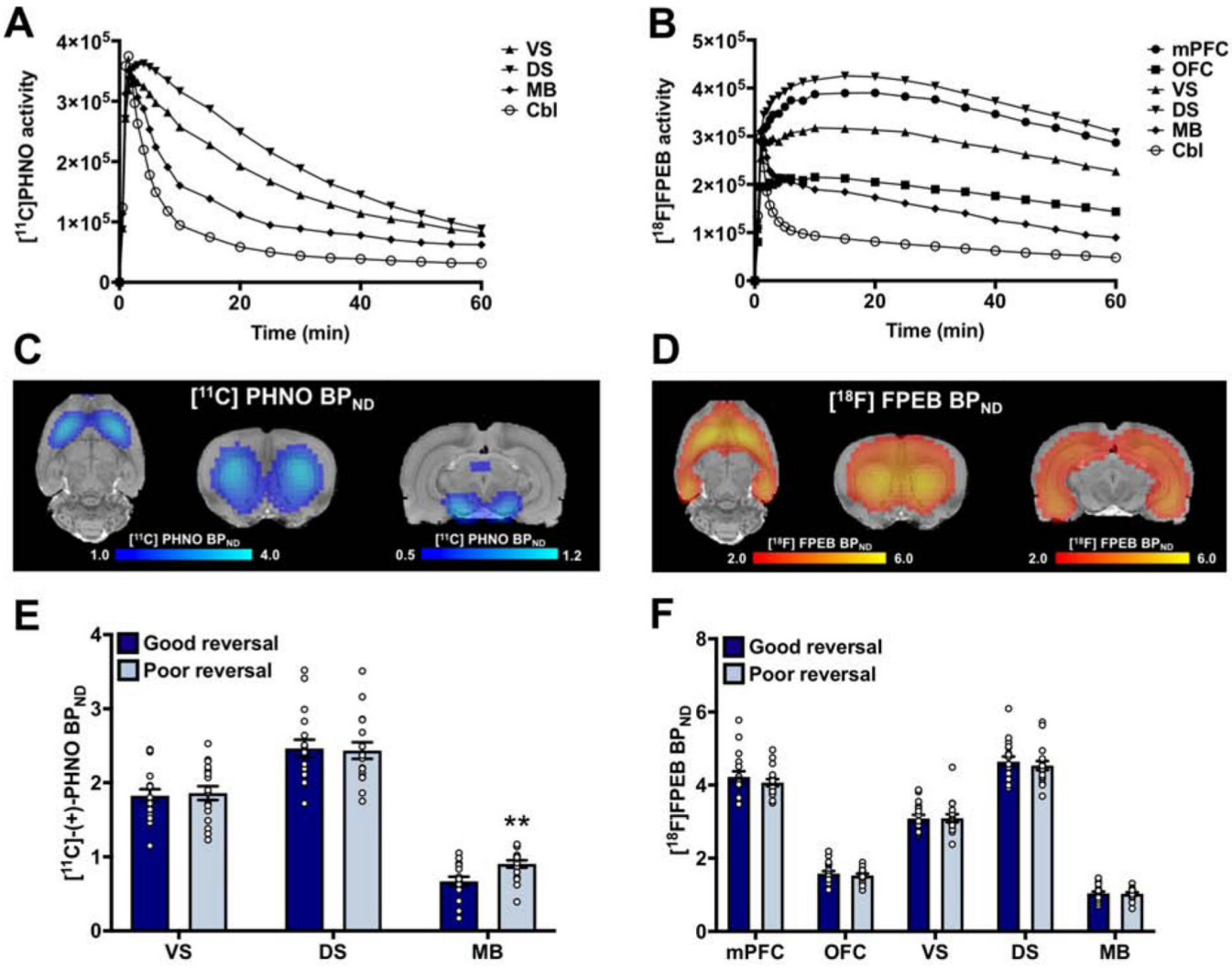

Figure 3:

Poor reversal performance is associated with higher midbrain D_3 BP_{ND}. (A-B) Average time activity curves in the six regions of interest extracted from either (A) [^{11}C]PHNO or (B) [^{18}F]FPEB dynamic images. (C-D) Binding potential maps showing the distribution of (C) [^{11}C]PHNO and (D) [^{18}F]FPEB binding in the rat brain. (E) [^{11}C]PHNO BP_{ND} in the midbrain was significantly greater in the poor reversal group compared to good reversal group. (F) No differences in [^{18}F]FPEB BP_{ND} were observed between good and poor reversal groups. ** $p<0.01$; Abbreviations: mPFC – medial prefrontal cortex; OFC – orbitofrontal cortex; VS – ventral striatum; DS – dorsal striatum; MB – midbrain; Cbl – cerebellum.

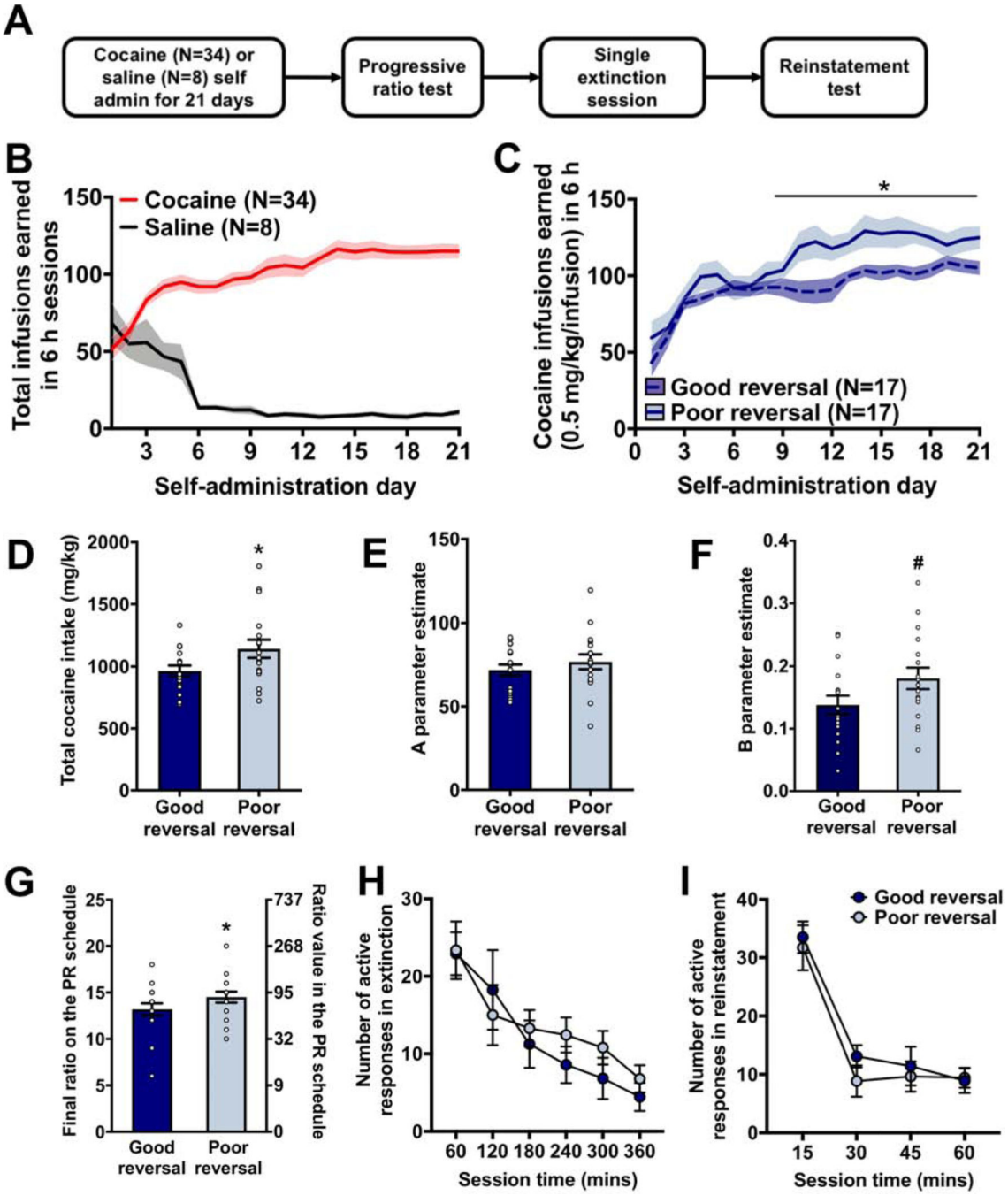

Figure 4:

Poor reversal performance is associated with a greater escalation in cocaine intake. (A) The behavioral experiments used for assessing addiction-relevant behaviors. (B) The number of infusions earned increased in the cocaine self-administration group and decreased in the saline self-administration group across the 21 6 h daily sessions. (C) The rate of increase in the number of cocaine infusions earned across the 21 self-administration sessions was significantly greater in the poor reversal group compared to the good reversal group. Group differences emerged on the 9th session and persisted until the 21st session. (D) The total

number of infusions earned across the 21 sessions was significantly greater in the poor reversal group compared to the good reversal group. (E-F) The power function revealed that initial cocaine reinforcement was similar between the good and poor reversal groups but that the (E) rate of escalation in cocaine self-administration was higher in the poor reversal group. (G) The final schedule achieved in the progressive ratio (PR) test was higher in the poor reversal group. No group differences were observed in the number of responses rats made in the extinction test (H) or in the cue-induced reinstatement test (I). * $p<0.05$.

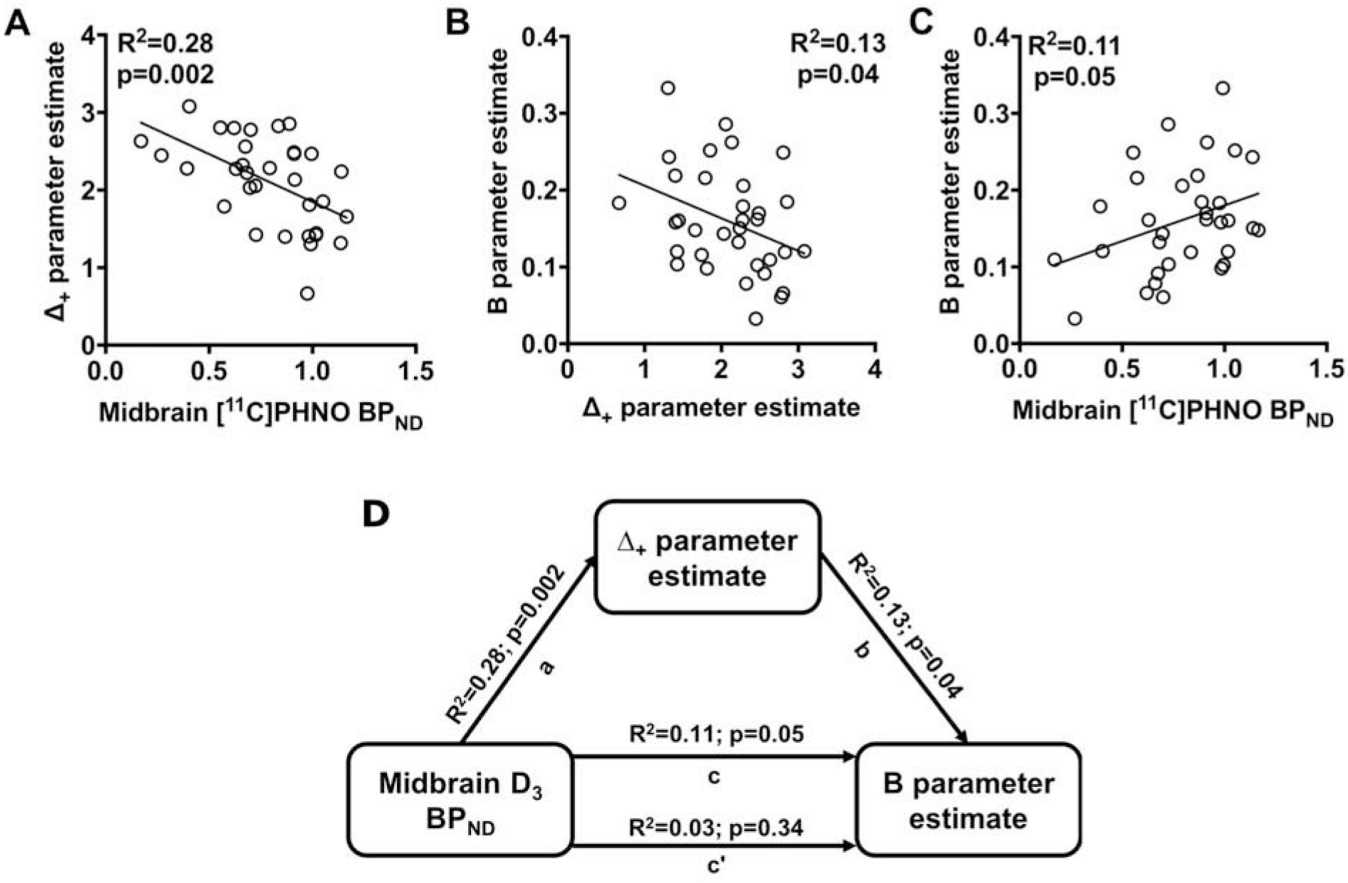

Figure 5:

Midbrain D3 receptor BP_{ND} is correlated with the Δ_+ parameter and the rate of escalation in cocaine intake. (A) Individual differences midbrain [^{11}C]-(+)-PHNO BP_{ND} are negatively correlated to variation in the Δ_+ parameter. (B) Variation in the Δ_+ parameter predicts the rate of escalation in cocaine intake (e.g., B parameter). (C) Midbrain [^{11}C]-(+)-PHNO BP_{ND} predicts the rate of escalation in cocaine intake (e.g., B parameter). (D) A causal mediation analysis of midbrain [^{11}C]-(+)-PHNO BP_{ND}, the Δ_+ parameter, and the rate of escalation in cocaine intake (e.g., B parameter). When the Δ_+ parameter is included as a mediator of the relationship between midbrain [^{11}C]-(+)-PHNO BP_{ND} and the B parameter, the strength of this relationship was reduced (path c'). However, the indirect was not significant suggesting that the Δ_+ parameter only partially mediated the relationship between [^{11}C]-(+)-PHNO BP_{ND} and the B parameter.

KEY RESOURCES TABLE

Resource Type	Specific Reagent or Resource	Source or Reference	Identifiers	Additional Information
Add additional rows as needed for each resource type	Include species and sex when applicable.	Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use “this paper” if new.	Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.	Include any additional information or notes if necessary.
Chemical Compound or Drug	Cocaine hydrochloride	NIDA Drug Supply		
Chemical Compound or Drug	[11C]-(+)-PHNO	Yale PET Center		Gallezot et al., 2012
Chemical Compound or Drug	[18F]FPEB	Yale PET Center		Hamill et al., 2015
Organism/Strain	Long Evans male rats	Charles River Laboratory	RRID:RGD_2308852	
Software; Algorithm	Matlab (2019a)	Mathworks	RRID:SCR_001622	
Software; Algorithm	Med PC	Med Associates	RRID:SCR_014721	