

BRIEF REPORT

Cued Reinstatement of Cocaine but Not Sucrose Seeking Is Dependent on Dopamine Signaling in Prelimbic Cortex and Is Associated with Recruitment of Prelimbic Neurons That Project to Contralateral Nucleus Accumbens Core

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Abstract

Background: Drug cues recruit prelimbic cortex neurons that project to ipsilateral nucleus accumbens core. However, it is not known if the same is true for prelimbic cortex projections that decussate to innervate contralateral nucleus accumbens core. Further, a role for prelimbic cortex dopamine signaling in cued reinstatement of cocaine seeking has not been shown.

Methods: We assessed Fos expression in prelimbic cortex neurons that project to contralateral nucleus accumbens core following cued reinstatement of cocaine or sucrose seeking. We also tested the effect of intra-prelimbic cortex infusions of the D1/D2 antagonist fluphenazine on cued cocaine and sucrose seeking.

Results: Prelimbic cortex-contralateral nucleus accumbens core projections were activated by cocaine cues but not sucrose cues, and this activation correlated with reinstatement behavior. Blockade of prelimbic cortex dopamine signaling prevented cued reinstatement of cocaine- but not sucrose-seeking behavior.

Conclusions: Cued cocaine seeking is associated with activation of the prelimbic cortex-contralateral nucleus accumbens core pathway. Prelimbic cortex dopamine signaling is necessary for cues to reinstate drug-seeking behavior.

Keywords: addiction, relapse, striatum, prefrontal cortex, self-administration

Introduction

Human neuroimaging studies show that cocaine-paired cues activate prefrontal cortex (PFC) in cocaine addicts (Wexler et

al., 2001) and that the magnitude of this activation is predictive of craving and relapse risk (Childress et al., 1999). Preclinical

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studies using the reinstatement model of relapse in rodents have provided significant insight into the functional specificity of PFC subregions recruited by drug cues. These studies have shown that prelimbic cortex (PL) is activated by cocaine-associated cues (Ciccocioppo et al., 2001; Zavala et al., 2008) and that inactivation of this region prevents cue-induced reinstatement of cocaine seeking (McLaughlin and See, 2003; Di Pietro et al., 2006).

A subset of PL neurons provides direct input to nucleus accumbens core (NAc), and optogenetic inhibition of these inputs attenuates cued reinstatement of cocaine seeking (Stefanik et al., 2013). The majority of PL neurons that provide input to NAc project ipsilaterally (NAc^{CiP^{SI}}) (Sesack et al., 1989); we recently showed that activation of these neurons by drug-associated stimuli is highly predictive of reinstatement behavior (McGlinchey et al., 2016). Interestingly, a smaller but significant proportion of PL-NAc projections decussate to innervate the contralateral NAc (NAc^{contra}) (Sesack et al., 1989). Although these contralateral projections may be functionally significant, their specific role in drug seeking has not been investigated. Thus, the first aim of the current study was to examine the extent to which PL-NAc^{contra} projections are activated by cues associated with cocaine. Because PL also responds to cues associated with natural rewards (Grimm et al., 2016), we also examined activation of the PL-NAc^{contra} pathway following cued reinstatement of sucrose seeking.

Rat PL receives dense dopaminergic (DA) input from ventral tegmental area (VTA) (Swanson, 1982), and TH+ fibers contact NAc-projecting PL neurons (Carr et al., 1999). Microinfusions of DA into PL reinstate cocaine-seeking behavior following extinction training (Park et al., 2002), whereas intra-PL infusions of DA receptor antagonists block reinstatement behavior elicited by a cocaine prime (McFarland and Kalivas, 2001) or foot-shock (Capriles et al., 2003). Surprisingly, a role for DA signaling in cued reinstatement of cocaine seeking has not been shown, despite evidence that the VTA dopamine system is recruited by stimuli associated with drugs and other rewards (Kufahl et al., 2009; Mahler and Aston-Jones, 2012). Thus, the second aim of this study was to examine the functional importance of PL DA signaling in cued reinstatement of cocaine- vs sucrose-seeking behavior.

Methods

Subjects

Male Sprague-Dawley rats (200–225 g; Charles River) were single-housed in a reverse 12-hour-light cycle. Animals were housed in temperature- and humidity-controlled animal facilities (AAALAC-accredited) in clear tub cages and had ad libitum access to food and water. Tissue from some animals in a previous study (McGlinchey et al., 2016) was used here, as detailed below. All procedures were approved by the Medical University of South Carolina and Rutgers University Institutional Animal Care and Use Committees.

Cocaine Self-Administration

Animals were trained to self-administer cocaine on a fixed ratio 1 schedule as described previously (see supplementary Information 1). Delivery of cocaine was paired with the activation of the white cue light above the active lever and a 2.9-kHz tone. After the last day of self-administration, rats underwent daily 2-hour extinction sessions in which responses on either lever were recorded but resulted in no infusion or light/tone

presentation. Animals continued under extinction conditions for a minimum of 7 d and until they reached a criterion of ≤ 25 active lever presses/session for 3 consecutive days. Control rats were tested with fixed ratio 1 sucrose self-administration (45 mg pellet, Test Diet; in central hopper) using parameters similar to those described above for cocaine.

Experiment 1: Fos Expression in PL-NAc^{contra} Pathway following Cued Cocaine or Sucrose Seeking

Immediately following implantation of the jugular catheter, rats received a unilateral microinjection of cholera toxin B subunit (CTb; ~40 nL, 0.5% dissolved in 0.1M phosphate buffer, Sigma) into NAc (AP: +1.3 mm, ML: ± 1.8 mm, DV: -7.8 from skull surface) using a glass micropipette attached to a Picospritzer. Pressure injections were made over a 2-minute period, and pipettes remained in place for 10 to 15 minutes to minimize diffusion along the pipette tract.

After 7 days recovery, rats were trained in self-administration and extinction as described above. Rats in the extinction group were given an additional 2-hour extinction test the day after reaching the extinction criteria. Reinstatement rats were tested for reinstatement the day after meeting extinction criteria, whereby responses on the active lever yielded the same tone/light presentations that had previously been paired with cocaine/sucrose, but no cocaine/sucrose delivery. Two hours after their extinction or reinstatement test session, rats were perfused and brains were processed for Fos and CTb immunolabeling using techniques described elsewhere (see supplementary Information 2). Quantification of Fos and CTb labeling was carried out in a subset (n=14 cocaine, n=14 sucrose) of rats previously identified to have received accurate injections of CTb into NAc (McGlinchey et al., 2016). Sections representing rostral/intermediate/caudal levels of PL (+3.24 to +2.76 mm from Bregma) were analyzed using a 16x objective on a Zeiss AxioZoom V16 microscope and then stitched together using Zen Imaging software. An observer blind to experimental conditions counted the total number of Fos+ neurons in both hemispheres of PL as well as the total number of CTb+ neurons and Fos+/CTb+ cells in PL contralateral to NAc CTb injections.

Experiment 2: Effect of Dopamine Receptor Blockade in PL on Cued Cocaine vs Sucrose Seeking

Following self-administration training, animals underwent stereotaxic surgery to implant bilateral 26G cannulae (Plastics One) 1 mm above the PL (AP: +3.00; ML: +0.75; DV: -2.90). Following 1 week recovery, rats were given 3 “reminder” self-administration sessions before undergoing extinction training as above. Following the final extinction session, animals were gently restrained, and bilateral injectors (28G, Plastics One) were lowered into the cannulae and inserted to 1 mm beyond the bottom of the cannulae into PL. The injectors were then removed without making any injections. The following day, using the same injectors, animals received either unilateral or bilateral infusions of either aCSF or fluphenazine (D1/D2 antagonist, Tocris Bioscience; 10 nmol/0.3 μ L over 1 minute). Injectors were held in place for 1 minute after the infusion to allow for complete diffusion of the injectate. Five minutes from the beginning of the infusion, animals were placed in the operant chamber and tested for reinstatement behavior as in Experiment 1. Animals underwent at least 2 days of extinction training (< 25 active lever presses) before being tested for reinstatement under the opposite drug condition. The order in

which animals received fluphenazine or aCSF was fully counter-balanced. The hemisphere in which animals received a unilateral injection was randomized across animals.

To explore possible nonspecific effects of PL dopamine antagonism, we assessed animals for general locomotor activity following unilateral/bilateral infusions of fluphenazine or vehicle using methods described previously (see supplementary Information 3).

Data Analysis

In Experiment 1, the percentage of CTb+ cells that expressed Fos was calculated for each tissue section (only sections that contained CTb+ cells were analyzed), means were computed across all sections for each rat ($n=7$ rats/group), and these per rat means were averaged across behavioral groups. Total Fos and %CTb+ cells that were also Fos+ were compared across groups using an independent-samples t test or, if not normally distributed (assessed by the Shapiro-Wilk test), a Mann Whitney test. In Experiment 2, reinstatement of active lever responding following unilateral/bilateral fluphenazine was compared with vehicle treatment and extinction responding using RM-ANOVA, and subsequent posthoc tests where appropriate. Graphpad Prism V6 and an α value of 0.05 was used for all analyses.

Results

Experiment 1: PL Neurons That Project to NAcC^{contra} Are Activated following Cued Cocaine but Not Sucrose Seeking

Data for self-administration training, extinction, and reinstatement testing for cocaine and sucrose groups are reported

elsewhere (McGlinchey et al., 2016). Data reported here are from a subgroup of rats in that prior report that received CTb injections in NAcC. Rats in this subgroup showed stable self-administration and extinction learning similar to that of the greater cohort (see supplementary Information 4).

We first compared Fos expression in PL following cued reinstatement of cocaine or sucrose seeking (Figure 1A-B). We observed significantly more Fos+ neurons in PL following cocaine reinstatement compared with extinction ($t(12)=2.194$, $P=.049$) (Figure 1D). There was no significant correlation between PL Fos expression and reinstatement scores ($R^2=0.111$, $P>.05$; data not shown). Sucrose rats showed a similar trend, with increased Fos in PL following cued reinstatement compared with extinction, $t(12)=3.470$, $P=.005$ (Figure 1E). There was no correlation between PL Fos expression and sucrose reinstatement behavior ($R^2=0.183$, $P>.05$; data not shown).

Next, we quantified the percentage of CTb+ cells in PL contralateral to NAcC CTb injections that also expressed Fos following reinstatement. We observed an average total of 29 ± 6 and 37 ± 6 CTb+ cells/section in cocaine and sucrose rats, respectively. This equated to an overall average of 33 ± 4 CTb+ cells/section across all animals. Schematics of CTb injection sites from both cocaine and sucrose groups are presented in McGlinchey et al., (2016). In cocaine animals, $8.7\pm 2.3\%$ of CTb+ neurons also expressed Fos following reinstatement, which was significantly greater than in extinction animals ($3.4\pm 1.0\%$; data not normally distributed, $P<.01$; Mann Whitney comparison, $P=.017$; Figure 1F). In contrast, sucrose reinstatement was not associated with a significant recruitment of the PL-NAcC^{contra} pathway ($t(12)=1.850$, $P=.089$) (Figure 1G). Notably, in cocaine rats, activation of the PL-NAcC^{contra} pathway was positively correlated with cocaine

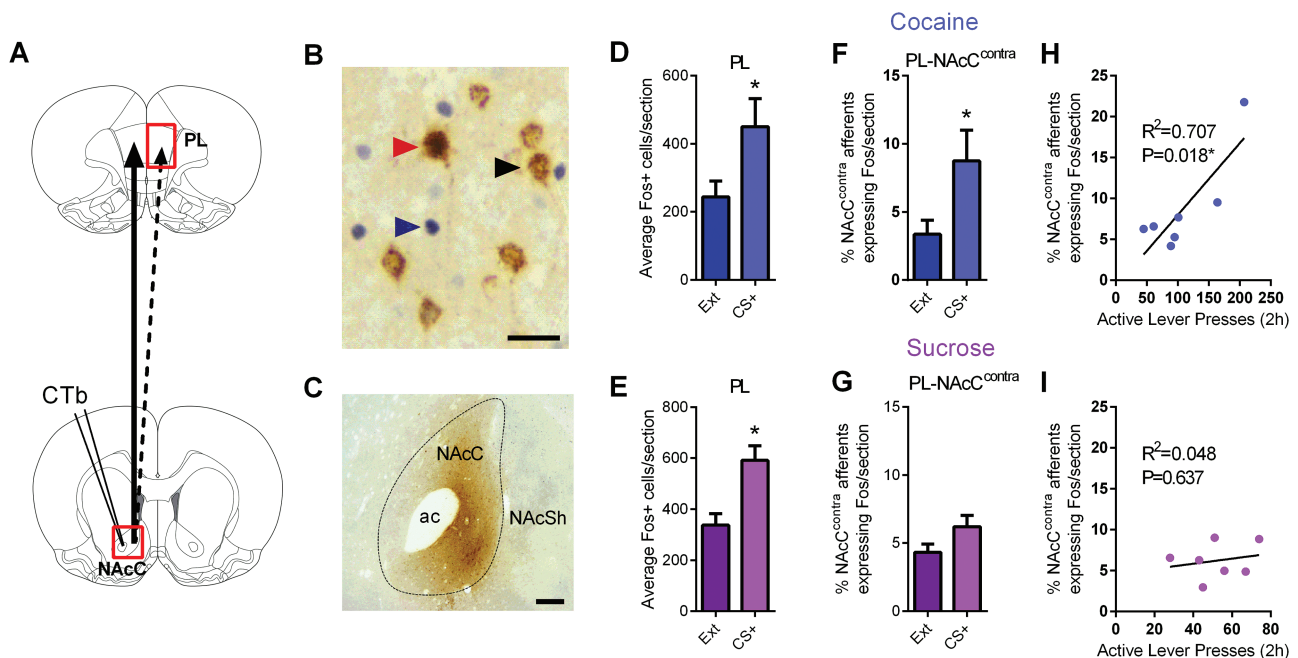


Figure 1. Cued reinstatement of cocaine seeking is associated with recruitment of prefrontal cortex (PL)-contralateral nucleus accumbens core (NAcC^{contra}) projections. (A) Rats received unilateral injections of the retrograde tracer cholera toxin B into NAcC, and CTb and Fos were examined in contralateral PL following cued reinstatement testing, thus identifying activation of those PL cells that project to NAcC^{contra}. (B) Representative image of CTb-only (black arrow), Fos-only (blue), and CTb+Fos (red) labeled neurons in PL. Scale bar = 50 μ m. (C) Representative image showing CTb deposit in NAcC. Scale bar = 200 μ m. (D) Cued reinstatement of cocaine seeking was associated with a significant increase in Fos+ neurons in PL relative to extinction levels. (E) Similar to cocaine, cued reinstatement of sucrose seeking was associated with a significant increase in Fos+ neurons in PL compared with extinction levels. (F) Cued cocaine seeking was also associated with an increase in the %NAcC^{contra}-projecting PL neurons that were also Fos+ compared with extinction levels. (G) Cued sucrose seeking was not associated with a significant increase in the %NAcC^{contra}-projecting PL neurons that were also Fos+ compared with extinction levels. (H) In cocaine rats, activation of the PL-NAcC^{contra} pathway correlated with the magnitude of reinstatement behavior. (I) Fos expression in the PL-NAcC^{contra} pathway did not correlate with sucrose reinstatement behavior. $n=7$ rats for all groups. * $P<.05$. Error bars indicate SEM.

reinstatement behavior ($R^2=0.707$, $P=.018$) (Figure 1H). No such relationship was observed in sucrose rats ($R^2=0.048$, $P>.05$) (Figure 1I).

Experiment 2: Bilateral Blockade of Dopamine Signaling in PL Prevented Cued Cocaine but Not Sucrose Seeking.

In cocaine rats, we observed a significant reinstatement of active lever responding relative to extinction following microinjections of aCSF into PL ($P<.001$). There was a modest, nonsignificant suppression of cocaine reinstatement behavior following unilateral fluphenazine in PL ($F_{2,32}=8.680$, $P=.008$; posthoc test comparison $P=.073$) (Figure 2B). In contrast, bilateral infusions of fluphenazine resulted in a profound and significant attenuation of reinstatement behavior ($F_{2,23}=7.982$, $P=.016$; posthoc comparison $P=.037$) (Figure 2B). There was no effect of either unilateral or bilateral fluphenazine in PL on inactive lever responding ($P>.05$).

In sucrose rats, animals showed a significant reinstatement of responding on the active lever under vehicle conditions ($P<.001$) (Figure 2E). In contrast to cocaine animals, neither unilateral nor bilateral intra-PL infusions of fluphenazine affected responding on either the active or inactive lever ($P>.05$) (Figure 2E).

Neither unilateral nor bilateral fluphenazine affected the number of horizontal or vertical beam breaks animals made or the total distance travelled throughout the session ($P>.05$) (supplementary Information 5).

Discussion

PL has emerged as a critical component of relapse circuitry. A number of studies have reported enhanced markers of neural activity in PL following cued reinstatement of cocaine seeking (Ciccocioppo et al., 2001; Zavala et al., 2008; Kufahl et al., 2009), and inactivation of PL reduces reinstatement of cocaine seeking elicited by drug cues, stress, or a priming injection of cocaine (McFarland and Kalivas, 2001; Capriles et al., 2003; Stefanik et al., 2013). We provide further evidence for PL in cued reinstatement behavior by confirming enhanced Fos expression in cued reinstatement animals compared with extinction. Interestingly, we also observed increased PL Fos expression following cued reinstatement of sucrose seeking, indicating that PL may be generally responsive to stimuli associated with reward. Although this is the first report examining Fos expression in mPFC using the extinction-reinstatement model of sucrose seeking, a recent study reported that incubation of responding for sucrose-paired cues following forced abstinence is associated with enhanced Fos expression in PL (Grimm et al., 2016), further supporting a general role for this region in reward cue processing.

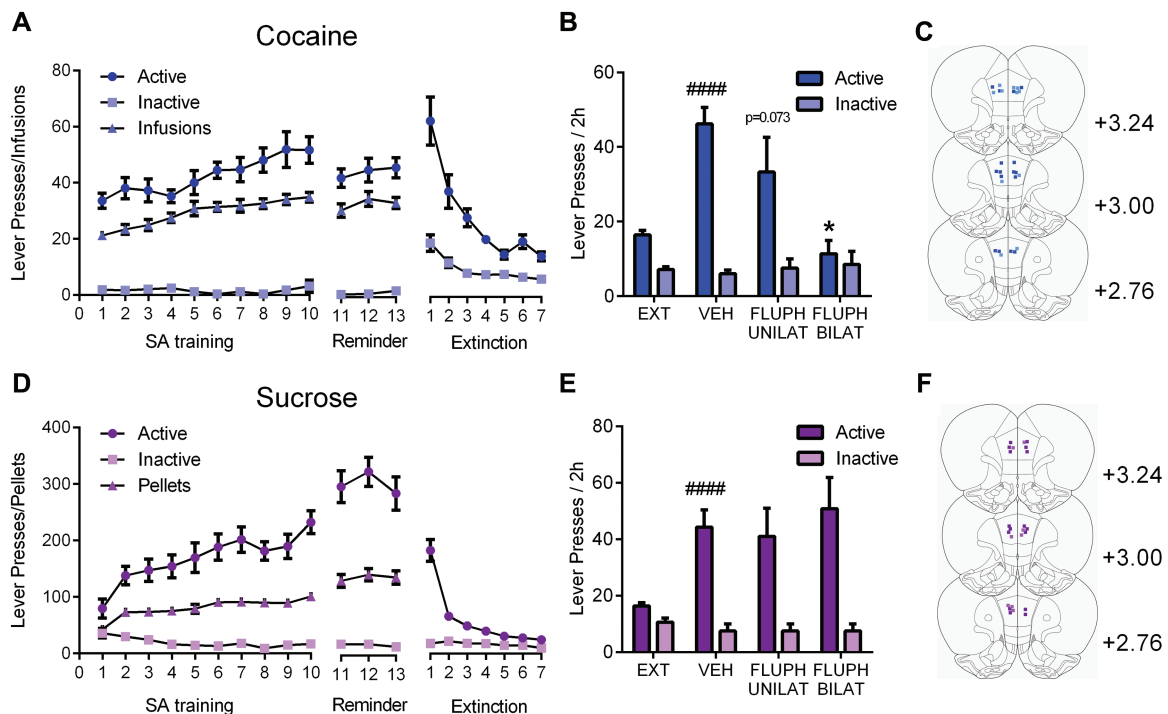


Figure 2. Blockade of dopamine signaling in prelimbic cortex (PL) attenuates cued cocaine but not sucrose seeking. (A) Rats were trained to self-administer cocaine over 10 days and then underwent surgery to implant guide cannulae above PL. Following 3 post-surgery reminder self-administration sessions, lever pressing was extinguished over at least 7 days. Data represent behavioral data averaged across all treatment groups ($n=19$). (B) EXT depicts the average number of active and inactive lever responses made over the final 3 extinction sessions across all animals ($n=19$). Following vehicle microinfusions into PL (VEH), rats showed a robust reinstatement of active lever responding for drug-associated stimuli. Reinstatement was not significantly affected by unilateral intra-PL infusions of the D1/D2 antagonist fluphenazine (FLUPH UNILAT; $n=11$), whereas bilateral intra-PL infusions of fluphenazine (FLUPH BILAT; $n=8$) completely blocked reinstatement. (C) Placements of microinjectors in PL for cocaine rats. Dark blue: bilateral infusions; light blue: unilateral infusions. (D) Rats were trained to lever press for sucrose pellets, given reminder self-administration sessions and then underwent extinction training in a similar manner to cocaine rats. Data represent behavioral data averaged across all treatment groups ($n=16$). (E) EXT depicts the average number of active and inactive lever responses made over the final 3 days of training for extinction of sucrose self-administration. Following vehicle microinfusions into PL, rats showed robust reinstatement of active lever responding in response to sucrose-associated stimuli. Neither unilateral ($n=9$) nor bilateral ($n=7$) intra-PL fluphenazine treatment affected reinstatement behavior. (F) Placements of microinjectors in PL for sucrose rats. Dark purple: bilateral infusions; light purple: unilateral infusions. $####P<.0001$ vs extinction. $*P<.05$ vs vehicle. Error bars indicate SEM.

Consistent with previous studies (Zavala et al., 2008; Kufahl et al., 2009), overall PL Fos expression was not associated with drug-seeking behavior. This likely reflects the fact that PL contains distinct neuronal subpopulations, characterized by differential anatomical connectivity, that play unique roles in various aspects of drug behavior (Moorman et al., 2015). We previously reported that PL cells that project to NAcC^{ipsi} are recruited by drug-associated stimuli (McGlinchey et al., 2016), whereas those that project to VTA^{ipsi} are not (Mahler and Aston-Jones, 2012). Here, we examined whether drug cues also recruit PL neurons that project to NAcC^{contra}; previous anatomical studies found that this is a substantial projection. We observed 33±4 PL neurons per section that projected to NAcC^{contra}, compared with our previous observation of 93±14 that project to NAcC^{ipsi} (McGlinchey et al., 2016), indicating that in our hands, contralateral projections made up approximately 26% of all PL-NAcC projections. A significantly higher proportion of these PL-NAcC^{contra} projections was activated after cued cocaine reinstatement compared with extinction, and this activation was correlated with reinstatement responding. This is in contrast to cued sucrose seeking, which was not associated with recruitment of the PL-NAcC^{contra} pathway, indicating a potentially unique role for this pathway in drug-seeking behaviors. Although studies have shown that PL-NAcC projections are critical for reinstatement behavior (McFarland et al., 2003; Stefanik et al., 2013; Martin-Garcia et al., 2014), the roles of ipsilateral vs contralateral projections have not been reported. It is likely that the functional contribution of each projection is consistent with its relative strength (i.e., a stronger role for PL-NAcC^{ipsi} projections); however, this will need to be tested directly using techniques that allow for the simultaneous inhibition of both sets of PL-NAcC^{contra} projections while leaving PL-NAcC^{ipsi} projections intact.

PL is innervated by DA terminals arising from VTA, and viral overexpression of D1 receptors in PL enhances drug-cue associations (Sonntag et al., 2014). However, a role for DA signaling in PL in cued cocaine seeking has not been reported. Here, we show that bilateral intra-PL infusions of the D1/D2 antagonist fluphenazine block reinstatement of cocaine seeking elicited by drug-associated cues. This adds to previous studies that found that cocaine-primed and stress-induced reinstatement of cocaine seeking are prevented by intra-PL infusions of dopamine receptor antagonists (McFarland and Kalivas, 2001; Capriles et al., 2003), indicating that the DA-PL pathway is common across multiple modalities of relapse behavior. Our observation also aligns with evidence that intra-PL microinfusions of the selective D1 receptor antagonist SCH23390 block-cued heroin seeking, pointing to a role for this pathway across multiple drugs of abuse (See, 2009). This pathway appears to be unique to drug-seeking behavior, as intra-PL fluphenazine treatment had no effect on cued sucrose seeking. This may reflect plasticity within the DA-PL pathway following repeated drug exposure; future studies will be required to test this hypothesis.

Importantly, with respect to our anatomical findings, TH+ terminals arising from VTA contact PL cells that project to NAcC (Carr et al., 1999) as well as PL GABAergic interneurons (Sesack et al., 1995), indicating that DA can influence the PL-NAcC pathway both directly and indirectly. We previously found that the PL-NAcC^{ipsi} pathway is recruited in a DA-dependent manner to drive cued reinstatement of cocaine seeking (McGlinchey et al., 2016). In addition, optogenetic stimulation of VTA terminals in PL produces plasticity in PL neurons projecting to NAcC^{ipsi} (Buchta et al., 2017). It is unclear to what extent TH+ terminals make contact with NAcC^{contra}-projecting PL neurons, nor has the functional importance of this pathway in reinstatement

behavior been directly investigated. Again, further studies are required to address these questions.

In sum, we show that cued reinstatement of cocaine but not sucrose seeking is associated with recruitment of PL neurons that project to NAcC^{contra}. Whilst not tested directly, our correlation data indicate this activation of the PL-NAcC^{contra} pathway may contribute to cocaine reinstatement behavior. We also show that bilateral blockade of DA signaling in PL prevents reinstatement of cocaine but not sucrose seeking. Together with previous studies that show DA in PL is important for other forms of reinstatement, our data highlight this system as a potential target for therapeutic strategies designed to reduce relapse risk.

Supplementary Material

Supplementary data are available at *International Journal of Neuropsychopharmacology* online.

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Statement of Interest

None.

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