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Baseline-Dependent Effects of Cocaine Pre-Exposure on Impulsivity and $D_{2/3}$ Receptor Availability in the Rat Striatum: Possible Relevance to the Attention-Deficit Hyperactivity Syndrome

Daniele Caprioli[1,2], Young T Hong[3], Stephen J Sawiak[1,3], Valentina Ferrari[3], David J Williamson[3], Bianca Jupp[1,2], T Adrian Carpenter[1,3], Franklin I Aigbirhio[1,3], Barry J Everitt[1,2], Trevor W Robbins[1,2], Tim D Fryer[1,3] and Jeffrey W Dalley*[,1,2,4]

[1]Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK; [2]Department of Psychology, University of Cambridge, Cambridge, UK; [3]Department of Clinical Neurosciences, University of Cambridge, Wolfson Brain Imaging Centre, Cambridge Biomedical Campus, Cambridge, UK; [4]Department of Psychiatry, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK

We have previously shown that impulsivity in rats predicts the emergence of compulsive cocaine seeking and taking, and is coupled to decreased $D_{2/3}$ receptor availability in the ventral striatum. As withdrawal from cocaine normalises high impulsivity in rats, we investigated, using positron emission tomography (PET), the effects of response-contingent cocaine administration on $D_{2/3}$ receptor availability in the striatum. Rats were screened for impulsive behavior on the five-choice serial reaction time task. After a baseline PET scan with the $D_{2/3}$ ligand [^{18}F]fallypride, rats were trained to self-administer cocaine for 15 days under a long-access schedule. As a follow-up, rats were assessed for impulsivity and underwent a second [^{18}F]fallypride PET scan. At baseline, we found that $D_{2/3}$ receptor availability was significantly lower in the left, but not right, ventral striatum of high-impulsive rats compared with low-impulsive rats. While the number of self-administered cocaine infusions was not different between the two impulsivity groups, impulsivity selectively decreased in high-impulsive rats withdrawn from cocaine. This effect was accompanied by a significant increase in $D_{2/3}$ receptor availability in the left, but not right, ventral striatum. We further report that $D_{2/3}$ receptor availability was inversely related to baseline $D_{2/3}$ receptor availability in the ventral striatum of high-impulsive rats, as well as to the left and right dorsal striatum of both low-impulsive and high-impulsive rats. These findings indicate that the reduction in impulsivity in high-impulsive rats by prior cocaine exposure may be mediated by a selective correction of deficient $D_{2/3}$ receptor availability in the ventral striatum. A similar baseline-dependent mechanism may account for the therapeutic effects of stimulant drugs in clinical disorders such as ADHD.
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INTRODUCTION

Extreme and persistent forms of impulsive behavior are often present in addiction, hypothetically emerging from chronic substance abuse and/or as a pre-existing vulnerability trait marker (Dalley *et al*, 2011; Jentsch and Taylor, 1999; Verdejo-Garcia *et al*, 2008). The neural basis of increased impulsivity in drug addicts is poorly understood but concordant evidence implicates abnormalities in fronto-striatal ganglia circuitry, together with impaired dopamine (DA) neurotransmission in fronto-striatal networks (Koob and Volkow, 2010; Swanson *et al*, 2007). The most robust neural consequence of individuals being exposed to the stimulant drug cocaine, is a reduction in DA $D_{2/3}$ receptors in the striatum (Lee *et al*, 2009; Volkow *et al*, 2001; Volkow *et al*, 1993), an effect arising most parsimoniously as a direct response to chronic drug exposure itself (Dalley *et al*, 2008; Groman *et al*, 2012; Nader *et al*, 2006). However, dysfunction of $D_{2/3}$ receptors is also present before drug exposure in both experimental animals and humans that express high levels of impulsive behavior (Buckholtz *et al*, 2010; Dalley *et al*, 2007a). Thus, impaired $D_{2/3}$ receptor signalling may underlie impulsive behavior and be a susceptibility marker that is further compromised by chronic drug abuse.

A clear prediction arising from the work above is that chronic drug exposure in impulsive subjects will produce an

*Correspondence: Dr JW Dalley, Department of Psychology, University of Cambridge, Downing St, Cambridge CB2 3EB, UK. Tel: +44 0 1223 765 291; Fax: +44 0 1223 333 564. E-mail: jwd20@cam.ac.uk
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additional decrement in $D_{2/3}$ receptor availability in the striatum, notably in the nucleus accumbens, a key brain area involved in regulating impulse control (Basar *et al*, 2010; Dalley *et al*, 2011). As $D_{2/3}$ receptor availability is decreased in the ventral striatum of high-impulsive (HI) rats (Dalley *et al*, 2007a), exposure of impulsive animals to cocaine should further diminish $D_{2/3}$ receptor availability in the ventral striatum and thereby exacerbate impulsivity. Previous research, however, found that impulsivity was strongly decreased in HI rats withdrawn from intravenous cocaine self-administration (Dalley *et al*, 2007a; Everitt *et al*, 2008) and this intervention either had no effect (Dalley *et al*, 2005a) or transiently increased impulsivity (Winstanley *et al*, 2009) in low-impulsive (LI) rats. These findings suggest that baseline differences in impulsive behavior and $D_{2/3}$ receptor availability in the ventral striatum may be critical variables in shaping the ensuing effects of cocaine on response inhibitory control mechanisms. Elucidating the mechanism underlying this interaction may also be relevant to the clinical efficacy of stimulant drugs in clinical disorders of impulse control such as attention-deficit/hyperactivity disorder (ADHD). Furthermore, because ADHD represents a significant risk factor for substance use disorder, (Lee *et al*, 2011; van Emmerik-van Oortmerssen *et al*, 2012) this study has relevance for elucidating the etiological basis of vulnerability mechanisms underlying addiction. In the present study, we therefore investigated the consequences of cocaine exposure on $D_{2/3}$ receptor availability in the ventral striatum in relation to behavioral impulsivity on the five-choice serial reaction time task (five-CSRTT). High impulsivity on this paradigm is measured by the number of anticipatory responses to an imminent visual signal and is analogous to false alarms on the analogous continuous performance test in humans (Robbins, 2002). We used positron emission tomography (PET) and the selective high-affinity $D_{2/3}$ receptor antagonist [^{18}F]fallypride (Mukherjee *et al*, 1995) to assess $D_{2/3}$ receptor availability in the dorsal and ventral striatum, both before, and following exposure of rats to intravenous cocaine self-administration. In parallel, we investigated the relationship between behavioral impulsivity in selected LI and HI rats and changes in $D_{2/3}$ receptor availability in the ventral striatum following the discontinuation of cocaine self-administration.

MATERIALS AND METHODS

Subjects

Ninety-six adult male Lister-hooded rats (Charles River, Margate, UK), weighing 250–275 g and 2–3 months of age at the beginning of behavioral training, were used in this study. These were housed in groups of four in enclosed ventilation chambers during the training and selection of HI and LI rats. Upon completion of the screening and for the remaining period of the study, rats were singly housed ($n = 10$ HI; $n = 12$ LI). One cohort of rats was assigned to the cocaine self-administration experiment ($n = 6$ HI; $n = 8$ LI), while a second age-matched group of rats ($n = 4$ HI; $n = 4$ LI) was maintained for an equivalent period of time as the first group but did not receive cocaine. The holding room was humidity- and temperature-controlled (22 °C), and rats were maintained under a reversed 12-h light/dark cycle (white lights off/red lights on at 07:00 hours). Food was restricted to maintain body weights at 85–90% of free-feeding weights. Water was available *ad libitum*. All experiments conformed to the UK Animals (Scientific Procedures) Act of 1986 and local ethical guidelines. A timeline of experimental procedures is shown in Figure 1.

Five-Choice Serial Reaction Time Task

The apparatus consisted of 12 five-choice chambers (25 × 25 × 25 cm; Med Associates, St Albans, VT), each enclosed in a ventilated wooden sound-attenuating cubicle and illuminated by a house-light. The front wall of the chamber was curved with five equally-spaced 2.5 cm square apertures equipped with infrared detectors and a 3W LED located at the rear. A food magazine with infrared detectors at the entrance was set in the rear wall, into which 45 mg reward pellets were delivered (Noyes dustless pellets, Research Diets, UK). The chambers were controlled by a PC using WhiskerServer software (version 2.8) and a Five-Choice client (Cardinal and Aitken, 2010).

Rats were trained on the five-CSRTT over ~50 daily sessions (six sessions per week) to detect the location of a brief visual stimulus (0.7 s) presented on a random basis in one of the five recesses. Each session consisted of 100 discrete trials and lasted for ~30 min. Rats were advanced through 10 stages by steadily reducing the stimulus duration (Bari *et al*, 2008). Training was considered complete when rats responded to the target stimuli of duration 0.7 s with an accuracy of 75% and omissions on fewer than 20% of trials. Trials were initiated by subjects entering the magazine. After a fixed inter-trial interval (ITI) of 5 s, a visual stimulus was presented in a single aperture. Rats were rewarded with a single pellet if they correctly located the position of the target stimulus (a 'correct' response). A failure to respond within a limited hold period of 5 s was deemed an 'omission' and was signalled by a 5 s time-out period and a loss of food reward on that trial. Similar feedback was given on trials where rats responded in an adjacent aperture (an 'incorrect' response) or before the onset of the light stimulus (a 'premature' response). Behavioral performance was assessed by choice accuracy (% correct responses/(correct + incorrect trials); premature responding (% premature responses/(correct + incorrect + omission trials); omissions (% omission trials/(correct + incorrect + omission trials); latency to collect food (time from nose-poke response to entering the magazine, ms); correct response latency (time to make a response in the correct aperture after the onset of the light stimulus).

Rats were selected for high impulsivity using three long-ITI challenge sessions spaced 1 week apart (Dalley *et al*, 2007a). Challenge sessions ended after the completion of 100 discrete trials or when 60 min had elapsed. Note that all animals included in the present study completed 100 trials within the allotted time period (both before and after cocaine). HI rats were defined as those exhibiting a level of premature responding >50% on all three long-ITI sessions. LI rats were selected from the remaining rats and typically responded prematurely in fewer than 30% of trials during the long-ITI sessions.

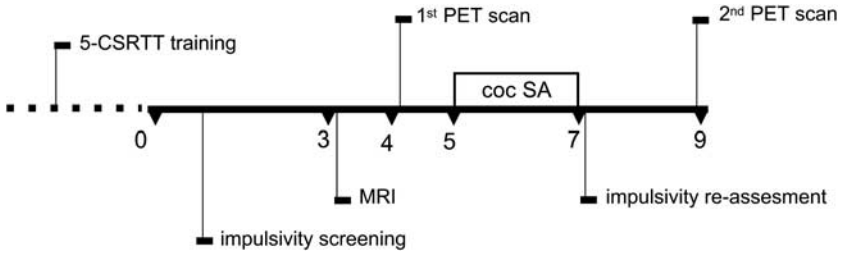

Figure 1 Timeline of experimental procedures in rats expressing differential levels of impulsive behavior on the five-choice serial reaction time task (five-CSRTT). Rats were trained for ~3 months before impulsivity screening. Values shown are in weeks.

Intravenous Cocaine Self-Administration

Intravenous cocaine self-administration was carried out using six operant chambers (31.8 × 25.4 × 26.7 cm; Med Associates, St Albans, VT), each enclosed within a ventilated wooden sound attenuating cubicle. The chambers were equipped with two, 4 cm wide retractable levers, positioned 12 cm apart and 8 cm from the grid floor (designated 'active' and 'inactive' levers). A stimulus light (2.5 W, 24 V) was positioned 2.5 cm above each lever. The chamber was illuminated by a house light (2.5 W, 24 V) positioned on the opposite wall to the levers. The chambers were controlled by a PC using WhiskerServer software (version 2.8) and a Second Order client (Cardinal *et al*, 2010).

Rats were implanted with a chronic indwelling catheter (CamCaths, Cambridge, UK) in the right jugular vein under isoflurane-induced anaesthesia. The catheter was externalized through a small incision on the dorsum between the scapulae. Rats were housed singly in their home-cages for 1 week to recover from surgery. Following MRI and a baseline [^{18}F]fallypride PET scan (see below, and Figure 1), rats were trained to acquire intravenous cocaine self-administration over 5 consecutive days under a fixed-ratio-1 schedule of reinforcement. During this phase every response on the active lever resulted in a 0.1 ml infusion of sterile saline containing 0.25 mg cocaine hydrochloride (McFarlan-Smith, Edinburgh, UK). Following each cocaine infusion the active lever was retracted for 20 s, the cue light above the lever was illuminated, and the house light was extinguished. After 20 s had elapsed, the active lever was extended into the chamber, responding on which resulted in a further infusion of cocaine. Responses on the inactive lever had no effect but were recorded. During this phase, access to cocaine was restricted to 50 infusions within each 6-h training period. Thereafter, access to cocaine was increased to 150 infusions during each 6-h session on days 6–15.

Post-Cocaine Behavioral Assessment

As a follow-up, HI and LI rats were retested on the five-CSRTT 2 weeks after the final cocaine self-administration session. This was carefully staggered to ensure that the behavioral assessment was carried out at the same time for all the rats after their last exposure to cocaine. Previous studies in our laboratory have established that behavioral performance on the five-CSRTT is severely disrupted for a period of about 7 days after the withdrawal from cocaine self-administration (Dalley *et al*, 2005a; Dalley *et al*, 2005b). We therefore assessed behavioral performance and $D_{2/3}$ receptor availability 2 weeks after the last cocaine self-administration session when the acutely disruptive effects of cocaine withdrawal had dissipated thus revealing more stable and potentially longer-lasting effects on behavior and dopamine receptor function (eg, as demonstrated by (Dalley *et al*, 2007b). Rats were initially run for two consecutive daily sessions with a fixed ITI of 5 s. They were then challenged with a single long-ITI session (ITI = 7 s) involving 100 discrete trials and a maximum duration of 60 min. Within 24 h of this assessment, rats underwent a second [^{18}F]fallypride PET scan (see Figure 1).

Magnetic Resonance Imaging (MRI)

HI and LI rats were anesthetised with 5% isoflurane and transferred to the MRI suite where they were placed on a plastic sliding cradle equipped with atraumatic ear bars. General anesthesia was maintained *via* the delivery of 1.5% isoflurane through a tube in the incisor bar. Body temperature was maintained at 37 °C using a rectal thermometer. Blood oxygen saturation, heart rate and breathing rate were monitored and maintained within normal limits using a non-invasive mouseOX pulse-oximeter sensor (Starr Life Science Corp, Oakmont, PA) attached to the foot.

Rats were scanned *in vivo* using a 4.7T Bruker BioSpec 47/40 system (Bruker Corporation, Ettlingen, Germany) over 90 min. Parameters were chosen for optimal contrast between grey and white matter in the brain (TR/TE_{eff} 3500/45ms, ETL 16, NEX 1, $256 \times 256 \times 96$ FOV $38.4 \times 38.4 \times 1.08\,mm^3$, isotropic resolution $150\,\mu m^3$). A 72 mm birdcage resonator was used for transmission and signals were detected with a 20 mm diameter surface coil.

MRI images were segmented into grey and white matter using SPM5 (Wellcome Trust Centre of Neuroimaging, UCL, London, UK) and the SPMMouse toolbox (www.fil.ion.ucl.ac.uk/spm/). DARTEL (Ashburner and Friston, 2005) was used to create standard templates of grey and white matter and the resulting transformations were applied to the bias-corrected MR images. These transformed images were averaged to provide a high-resolution anatomical template. Regions of interest (ROI) were delineated using Analyze 8.1 (Mayo Clinic, MN). The striatum was divided into three bilateral regions of interest: posterior dorsal striatum, anterior dorsal striatum, and ventral striatum (see Figure 4a).

PET

HI and LI rats were scanned using [^{18}F]fallypride on two occasions; before intravenous cocaine self-administration and 2 weeks after the last cocaine self-administration

session, which coincided within 24 h of the assessment of impulsivity on the five-CSRTT (see Figure 1). One HI and one LI rat was scanned on each day with the order counterbalanced across the pre- and post-cocaine scanning sessions.

Rats were imaged for 3 h using a microPET Focus-220 scanner (Concorde Microsystems, Knoxville, TN). The rats were placed prone on the scanner bed and the head fixed in a custom-made plastic frame using ear bars and a bite bar. Anaesthesia and physiological measures (body temperature, heart rate, blood oxygen saturation, breathing rate) were maintained as described above. Before the injection of tracer, singles-mode transmission data were acquired for 515 s using a rotating ^{68}Ge point source ($\sim$20 MBq). An attenuation correction sinogram was produced from this scan and a blank scan of the same duration, with scatter correction applied. For all scans, [^{18}F]fallypride was injected intravenously over 30 s, followed by a 15 s heparin-saline flush. The injected [^{18}F]fallypride activity (4 to 70 MBq) was adjusted so that the total mass of labelled and unlabelled fallypride injected was 0.5 nmol/kg. Dynamic data were acquired in list-mode for a 350–650 keV energy window and a 6 ns timing window. Data were subsequently binned into sinograms for the following time frames: 6×10 s, 3×20 s, 6×30 s, 10×60 s, 10×120 s, 29×5 min. Corrections were applied for randoms, dead time, normalization, attenuation, and decay. Fourier rebinning (Defrise *et al*, 1997) was used to compress the 4D sinograms to 3D before reconstruction with 2D filtered back projection with a Hann window cutoff at the Nyquist frequency. The image voxel size was $0.95 \times 0.95 \times 0.80$ mm, with an array size of $128 \times 128 \times 95$. The reconstructed images were converted to kBq/ml using global and slice factors determined from imaging a uniform phantom filled with a [^{18}F]fluoride solution.

For each scan, a mean PET image was manually and rigidly registered to its own MR image, and each MR image was spatially normalized to the aforementioned MR template using SyN (Avants *et al*, 2008; Klein *et al*, 2009), part of the Advanced Normalization Tools (ANTS) package. By combining the rigid and non-rigid (spatial normalization) transforms, the PET images of each scan ($n = 64$) were aligned to the MR template. We verified that the ROI for each subject did not span the intended brain regions; thus our receptor availability measurements were not affected by individual differences in brain structure.

$D_{2/3}$ receptor availability was quantified using non-displaceable binding potential (BP_{ND}) (Innis *et al*, 2007), determined from reference tissue modeling with the cerebellum acting as the reference region. The borders of the reference region drawn on the MR template excluded the outermost lamina of the cerebellar cortex in order to avoid any partial volume error from uptake in the Purkinje cell layer. Regional BP_{ND} was estimated using the simplified reference tissue model (SRTM) (Lammertsma and Hume, 1996), while maps of BP_{ND} (used solely for illustrative purposes) were produced using implementation of the SRTM (Gunn *et al*, 1997).

Statistical Analysis

Behavioral data were subjected to analysis of variance (SPSS, version 17.0, Chicago, IL) using a general linear model with significance at $\alpha = 0.05$. Homogeneity of variance was verified using Levene's test. For repeated-measures analyses, Mauchly's test of sphericity was applied and the degrees of freedom corrected to more conservative values using the Huynh–Feldt epsilon for any terms involving factors, in which the sphericity assumption was violated. Differences in BP_{ND} between HI and LI rats were tested with repeated measures of analysis of variance. As previous research in our laboratory revealed asymmetry in $D_{2/3}$ receptor availability in the ventral striatum of HI rats (Jupp *et al*, 2013) we did not correct for multiple comparisons with hemispheric side. Thus, using *ex-vivo* autoradiography, we observed that [3H]raclopride binding was decreased collectively in the left, but not right nucleus accumbens core and shell of HI rats compared with LI rats. Pearson product moment correlations were used to assess the strength of the association between the change in BP_{ND} ((post-cocaine − pre-cocaine)/(pre-cocaine) × 100) and baseline BP_{ND} (pre-cocaine scan). All figures show group means ± 1 SEM. A William's test was used to evaluate differences between the two independent rho values in HI and LI, calculated separately for the left and right ventral striatum.

RESULTS

Impulsivity Phenotypes

The behavioral profiles of LI and HI rats on the five-CSRTT are shown in Figure 2. The percentage of premature responses for HI ($n = 6$) and LI ($n = 8$) rats, averaged across the three long-ITI challenge sessions, each spaced 1 week apart, was 73.8 ± 3.1% (mean ± SEM) and 23.4 ± 2.1%, respectively. HI rats were more impulsive than LI rats regardless of the ITI being set to the training interval of 5 s ('b1', 'b2', 'b3', 'b4', $P < 0.001$) or the challenge interval of 7 s ('LITI', $P < 0.001$). With the exception of attentional accuracy, which showed a significant decrease in HI rats relative to LI rats during the long ITI sessions (main effect of group: $F_{(1,12)} = 13.1$, $P = 0.004$) but not during the shorter ITI sessions (Table 1), no other behavioral variable was significantly altered in HI rats.

Intravenous Cocaine Self-Administration

Following MRI and baseline [^{18}F]fallypride PET scans (see Figure 1), both groups of rats were trained to self-administer cocaine by the intravenous route (Figure 3a). Two HI rats in the present study developed excessive rates of cocaine self-administration with subsequent adverse health effects that led to their removal from the study. HI and LI rats reliably self-administered cocaine during the first 5 days, when the daily number of infusions was restricted to 50 (ie, acquisition), and during the next 10 days, when access was increased to 150 daily infusions. No significant differences were observed in cocaine self-administration between LI and HI rats. The mean ± SEM number of cocaine infusions during the acquisition phase was: LI = 47.02 ± 1.2; HI = 48.5 ± 1.0, and during the long-access phase: LI = 134.8 ± 8.4; HI = 140.9 ± 3.3.

Post-Cocaine Behavioral Assessment

As a follow-up, HI and LI rats were reassessed for impulsivity and attentional performance on the five-CSRTT. It can be seen in Figure 3b that high impulsivity was profoundly reduced in HI rats withdrawn from cocaine self-administration (group × cocaine interaction: $F_{(1,12)} = 24.8$, $P < 0.001$, *post-hoc t*-test, $P < 0.001$). This effect was specific to premature responding in HI rats with no significant effects of cocaine exposure on omissions or the speed and accuracy of responding on the five-CSRTT (Figure 3b and Table 1). Furthermore, in a separate group of age-matched cocaine-naive HI rats ($n = 4$), we found no significant decline in impulsivity scores when rats where maintained for an equivalent period of time as those rats in the main study above (see Figure 3b insert and Table 1).

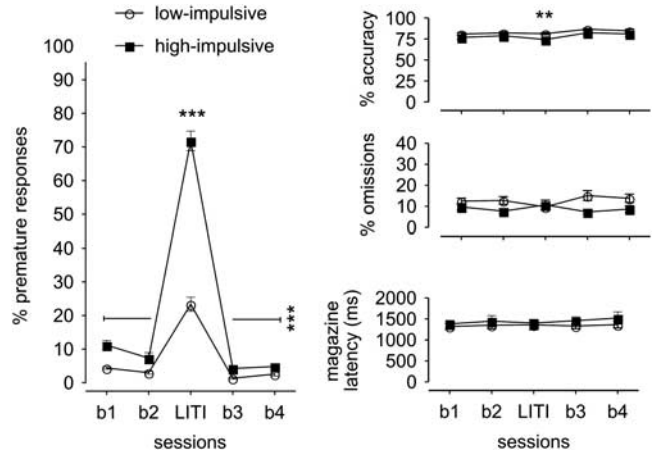

Figure 2 Screening for high impulsivity on the five-CSRTT. HI rats show an increased level of anticipatory responding compared with LI rats when the ITI is fixed at 5 s (baseline sessions: b1, b2, b3, b4) or 7 s (LITI) (LI $n = 8$; HI $n = 6$). HI rats are also less accurate than LI rats during long ITI sessions but show no differences in the number of omissions or latency to collect food reward. Selection of HI and LI rats involved 5 consecutive days of testing (b1, b2, LITI, b3, b4), repeated three times. The data shown (mean ± SEM) are averages of three consecutive test sessions in HI and LI rats (**$P < 0.01$, ***$P < 0.001$ HI *vs* LI).

$D_{2/3}$ Receptor Availability In The Ventral Striatum

Next we investigated $D_{2/3}$ receptor availability in the ventral striatum of LI and HI rats, both before cocaine self-administration ('pre-cocaine') and again 2 weeks after the last cocaine self-administration session, (ie, beyond the acute withdrawal period) when impulsivity had significantly decreased in HI rats ('post-cocaine'). We found a significantly lower $D_{2/3}$ receptor availability in the left ($t_{(12)} = 3.393$, $P = 0.005$) but not right ($t_{(12)} = 0.843$, $P = 0.416$) ventral striatum of drug-naive HI rats compared with LI rats (group × hemisphere interaction: $F_{(1,12)} = 4.9$, $P = 0.04$, Figure 4c). Following cocaine self-administration, this difference in $D_{2/3}$ receptor availability between LI and HI rats in the left ventral striatum was no longer evident ($t_{(12)} = -0.242$, $P = 0.813$), and remained non-significant in the right hemisphere ($t_{(12)} = 0.149$, $P = 0.884$). Thus, following cocaine exposure, only in the HI group did we observe a significant increase in $D_{2/3}$ receptor availability in the ventral striatum (pre-/post-cocaine × − side × group interaction: $F_{(1,12)} = 7.49$, $P < 0.05$; *post-hoc t*-test, $P < 0.05$). The mean ± SEM [^{18}F]fallypride BP_{ND} values for the left ventral

Table 1 Summary of the Effects of Intravenous Cocaine Self-administration on the Behavioral Performance of LI and HI Rats on the Five-CSRTT

	Cocaine				Cocaine-naive			
	Pre-		Post-		Pre-		Post-	
	LI ($n = 8$)	HI ($n = 6$)	LI ($n = 8$)	HI ($n = 6$)	LI ($n = 4$)	HI ($n = 4$)	LI ($n = 4$)	HI ($n = 4$)
SITI sessions								
% premature	2.8 ± 0.3	6.6 ± 0.5***	2.6 ± 0.3	4.6 ± 1.0	2.2 ± 0.7	5.1 ± 0.8	3.5 ± 1.5	9.2 ± 5.4
% accuracy	83.6 ± 1.2	78.5 ± 3.5	80.3 ± 2.7	81.2 ± 2.8	83.3 ± 3.2	78.3 ± 1.7	82.5 ± 1.9	78.5 ± 2.4
% omissions	13.5 ± 1.7	8.4 ± 1.2*	18.0 ± 3.9	22.4 ± 6.8	16.6 ± 3.2	11.7 ± 3.2	5.7 ± 1.4	12.1 ± 5.5
Magazine lat. (ms)	1342.5 ± 68.1	1452.6 ± 108.5	1143.8 ± 63.7	1626 ± 334.7	1057.3 ± 32.1	1613.8 ± 298.9	1104.3 ± 103.4	1246.9 ± 119.5
Correct lat. (ms)	751.6 ± 38.0	647.6 ± 40.1	842.4 ± 50.9	813.5 ± 78.9	802.3 ± 81.7	729.5 ± 62.1	714.8 ± 47.6	679.3 ± 35.3
LITI sessions								
% premature	23.4 ± 2.1	73.8 ± 3.1***	32.6 ± 5.6	32.8 ± 8.0[a]	19.9 ± 1.7	71.3 ± 11.2**	26.5 ± 1.8	80.6 ± 15.9*
% accuracy	81.4 ± 1.3	73.9 ± 1.6**	77.5 ± 1.5	76.1 ± 4.4	80.1 ± 1.6	74.2 ± 1.8	78.6 ± 2.2	74.6 ± 4.5
% omissions	9.7 ± 1.7	11.1 ± 2.7	11.1 ± 2.2	21.0 ± 5.3	13.0 ± 2.2	19.9 ± 4.5	8.7 ± 3.5	8.4.0 ± 1.2
Magazine lat. (ms)	1359.8 ± 115.8	1402.4 ± 86.9	1054.7 ± 51.3	1260.1 ± 107.3	1017.8 ± 42.6	1383.6 ± 178.5	1217.5 ± 272.8	1303.0 ± 117.8
Correct lat. (ms)	671.7 ± 38.6	589.4 ± 27.1	721.8 ± 63.2	710.2 ± 48.2	686.8 ± 64.9	616.3 ± 44.3	653.0 ± 33.2	608.7 ± 39.8

Abbreviations: HI, high-impulsive; LI, low-impulsive.
Shown are (mean ± SEM): % premature responses, % accuracy of responding, % omissions, magazine latencies (ms), and correct response latencies (ms) before ('Pre') and after ('Post') drug exposure or at equivalent time points for cocaine-naive animals. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ (LI *vs* HI).
[a](HI pre-cocaine *vs* HI post-cocaine).

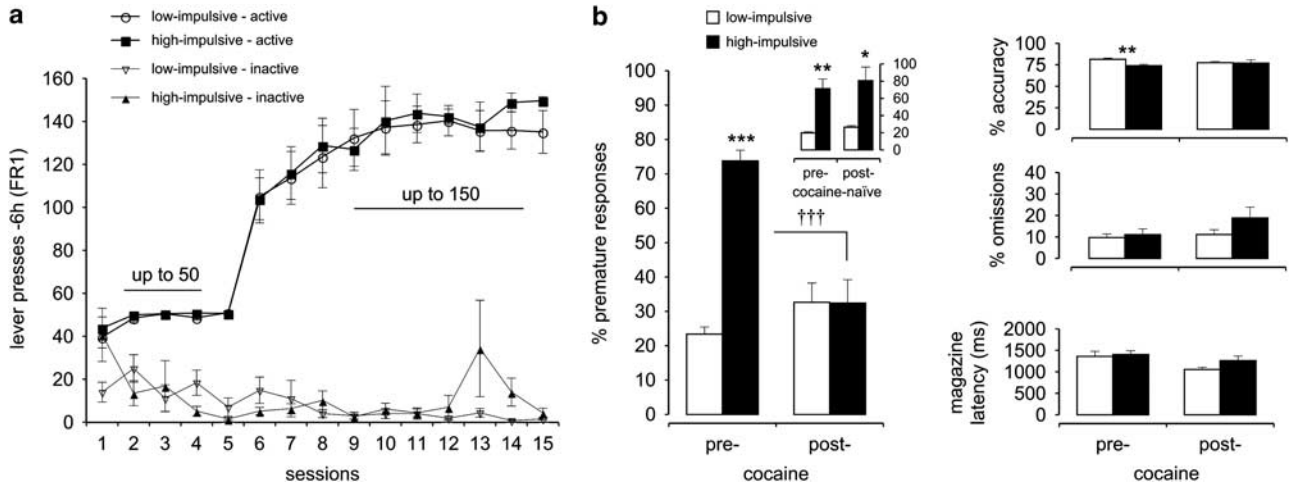

Figure 3 Selective correction of impulsivity in HI rats following withdrawal from intravenous cocaine self-administration. (a) Response-contingent cocaine administration in LI and HI rats under a continuous reinforcement schedule. Access to cocaine was restricted to 50 infusions during the first 5 days and 150 infusions during the subsequent 10 days (0.25 mg/infusion). Under this schedule there was no significant difference between LI and HI rats in the acquisition or maintenance of cocaine self-administration. (b) Behavioral effects of prior cocaine self-administration in LI (white bars) and HI (black bars) on the five-CSRTT. Pre-cocaine values are averaged across three weekly-spaced long ITI sessions (HI vs LI, $^{***}P<0.001$). Post-cocaine data are derived from a single long-ITI session administered 2 weeks after the last drug exposure day. It can be seen that HI rats withdrawn from cocaine show a selective reduction in premature responding compared with LI rats ($^{\dagger\dagger\dagger}P<0.001$). There were no significant effects of prior cocaine exposure on attentional accuracy, omissions or magazine latencies in HI and LI rats. The insert graph shows a separate group of age-matched but surgically- and cocaine-naive LI and HI rats (each $n=4$), which were tested and retested on the five-CSRTT at precisely the same interval as those rats in the main study. It can be seen that HI rats remain impulsive on this task throughout the duration of the study ($^{*}P<0.05$; $^{**}P<0.01$).

striatum in LI and HI rats, respectively, were 6.25 ± 0.18 and 5.36 ± 0.18 (pre-cocaine), and 6.18 ± 0.24 and 6.28 ± 0.39 (post-cocaine).

Baseline-Dependent Effects Of Cocaine On Striatal $D_{2/3}$ Receptors

Figure 5 shows individual [^{18}F]fallypride BP_{ND} values in the anterior and posterior dorsal striatum of LI and HI rats before and after cocaine self-administration. We found no significant group differences in $D_{2/3}$ receptor availability between LI and HI rats in either region, irrespective of cocaine exposure status. However, when we compared the change in [^{18}F]fallypride BP_{ND} before and after cocaine exposure we found that cocaine both increased and decreased [^{18}F]fallypride BP_{ND} depending on the baseline availability of $D_{2/3}$ receptors in the ventral and dorsal striatum (Figure 6). In the ventral striatum this effect was restricted to HI rats with a strong inverse relationship between the percentage change in [^{18}F]fallypride BP_{ND} and baseline [^{18}F]fallypride BP_{ND} in both the left ($r_{left} = -0.88$, $P=0.021$) and right ($r_{right} = -0.90$, $P=0.014$) hemisphere. Visual inspection of the data indicated the presence of an obvious outlier (figure 6a, right panel). However, when this subject was removed from the regression analysis we still observed a significant inverse relationship between the percentage change in [^{18}F]fallypride BP_{ND} and baseline [^{18}F]fallypride BP_{ND} in the ventral striatum regardless of impulsivity group ($r_{left} = -0.52$, $P=0.07$; $r_{right} = -0.65$, $P=0.016$). Moreover, individual changes in $D_{2/3}$ receptors availability did not significantly correlate with individual changes in impulsive behaviour (LI rats: $r_{left}=0.53$, $P=0.18$; $r_{right}=0.49$, $P=0.21$) (HI: $r_{left}=0.31$, $P=0.54$; $r_{right}=0.36$, $P=0.48$). In addition, there was no significant difference between the two independent correlation coefficients for the left and right ventral striatum (William's $test_{left}$ $z=1.1$, $P=0.86$; 1.0; William's $test_{right}$ $z=1.0$, $P=0.84$).

Post-cocaine baseline-dependent effects on $D_{2/3}$ receptor availability were also observed in the anterior and posterior dorsal striatum, which in these regions extended to LI rats as well. For all regions the relationship was strongly inversely related to baseline $D_{2/3}$ receptor availability (anterior dorsal striatum LI rats: $r_{left} = -0.78$, $P=0.02$; $r_{right} = -0.75$, $P=0.03$, HI rats: $r_{left} = -0.93$, $P=0.008$; $r_{right} = -0.91$, $P=0.01$; posterior dorsal striatum LI rats: $r_{left} = -0.86$, $P=0.006$, $r_{right} = -0.85$, $P=0.008$, HI rats: $r_{left} = -0.87$, $P=0.024$, $r_{right} = -0.91$, $P=0.01$).

DISCUSSION

Here we replicate and extend our previous finding of lower $D_{2/3}$ receptor availability in the ventral striatum of high-impulsive rats (Dalley *et al*, 2007a) by demonstrating that high impulsivity in rats is selectively reduced by prior exposure to response-contingent cocaine administration and that this effect is accompanied by a selective increase in $D_{2/3}$ receptor availability in the ventral striatum of high-impulsive rats compared with low-impulsive rats. Furthermore the observed decrease or increase in $D_{2/3}$ receptor availability in the striatum was baseline-dependent. Thus, when the pre-exposure binding potential of [^{18}F]fallypride was low, as was the case in the ventral striatum of high-impulsive rats, prior cocaine exposure and withdrawal had the effect of increasing $D_{2/3}$ receptor availability. In contrast, when baseline binding potential of [^{18}F]fallypride was high, we observed reduced $D_{2/3}$ receptor availability, an effect that was present throughout the ventral and dorsal

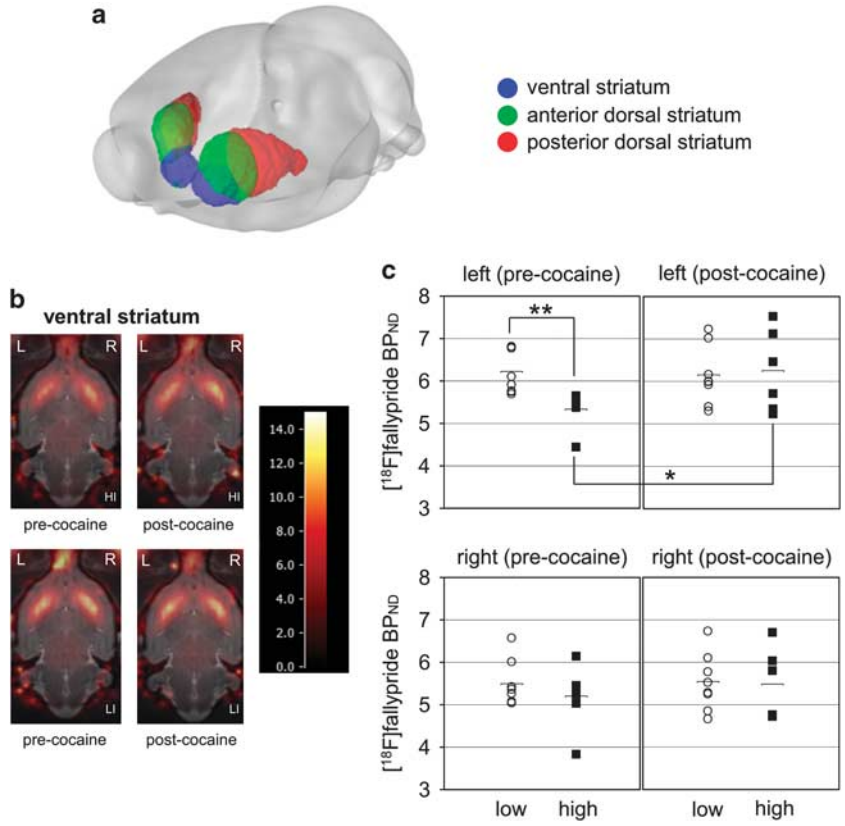

Figure 4 Selective remediation of deficient $D_{2/3}$ receptor availability in the left ventral striatum of HI rats by prior exposure to intravenous cocaine self-administration. (a) 3D depiction of regions of interest showing the ventral striatum (blue), anterior dorsal striatum (green), and posterior dorsal striatum (red). (b) Horizontal section through [^{18}F]fallypride BP_{ND} maps for HI and LI rats overlaid on the coregistered MR template (left (L) and right (R)). The images are 7 mm below the dorsal brain surface (BP_{ND} threshold = 14). (c) Binding potential (BP_{ND}) of [^{18}F]fallypride in the left and right ventral striatum of LI (square symbols, $n = 8$) and HI (circle symbols, $n = 6$) rats before ('pre-cocaine') and after ('post-cocaine') cocaine self-administration. It can be seen that [^{18}F]fallypride BP_{ND} is significantly reduced in the left ventral striatum of HI rats compared with LI rats before cocaine exposure (**$P < 0.01$) and that cocaine selectively normalises [^{18}F]fallypride BP_{ND} in HI rats in this brain region (*$P < 0.05$).

striatum. As high impulsivity was selectively reduced in rats with a recent prior history of cocaine self-administration, increased $D_{2/3}$ receptor availability in the ventral striatum may be a contributory mechanism underlying the reduction of impulsivity in high impulsive rats.

High-Impulsivity is Associated With Lower $D_{2/3}$ Receptors Availability in the Ventral Striatum and is Selectively Ameliorated by Prior Exposure to Cocaine

In line with previous results we show that low $D_{2/3}$ receptor availability in the ventral striatum is a latent phenotype of high impulsivity in rats. However, in our original study (Dalley *et al*, 2007a), this deficit was bilaterally expressed, whereas in the present study $D_{2/3}$ receptor availability was lower only in the left ventral striatum of HI rats compared with LI rats. The reason for this divergent result is unclear but may be due to methodological improvements made in the present study. Firstly, we rigidly registered PET images to individual MR images and non-rigidly registered these to a template MR image, whereas the previous approach involved rigid registration of PET to a template MR image. We also used an anatomical outline of the ventral striatum (Figure 4a) rather than a spherical region of interest and imaged the rats using a microPET Focus-220 scanner, which has a higher spatial resolution than the microPET P4 scanner used previously. Finally, we injected a higher radiotracer activity in the present study (mean 28 MBq *vs* 13 MBq), which coupled with the higher sensitivity of the Focus-220 compared with the P4, will have resulted in higher image signal-to-noise ratios. Collectively, these technical refinements would be expected to improve the precision and accuracy of [^{18}F]fallypride BP_{ND} estimation in the ventral striatum, and thereby confirm that low $D_{2/3}$ receptor availability in the ventral striatum is an endophenotype associated with high-impulsivity in rats.

Based on prior findings (Dalley *et al*, 2009; Groman *et al*, 2012; Nader *et al*, 2006), we predicted that prior cocaine exposure would further decrease $D_{2/3}$ receptors in the ventral striatum and exacerbate impulsivity. However, our results clearly show that withdrawal from cocaine self-administration both improves impulse control and restores $D_{2/3}$ receptor availability in this region, an effect that was strongly baseline-dependent. Although there was one obvious outlier in the high-impulsive group where baseline [^{18}F]fallypride BP_{ND} was low (~ 4), the general inverse relationship between baseline [^{18}F]fallypride BP_{ND} and the subsequent effects of cocaine on this index held in all striatal regions-of-interest, except the ventral striatum for LI rats. Thus, the baseline-dependent effects on

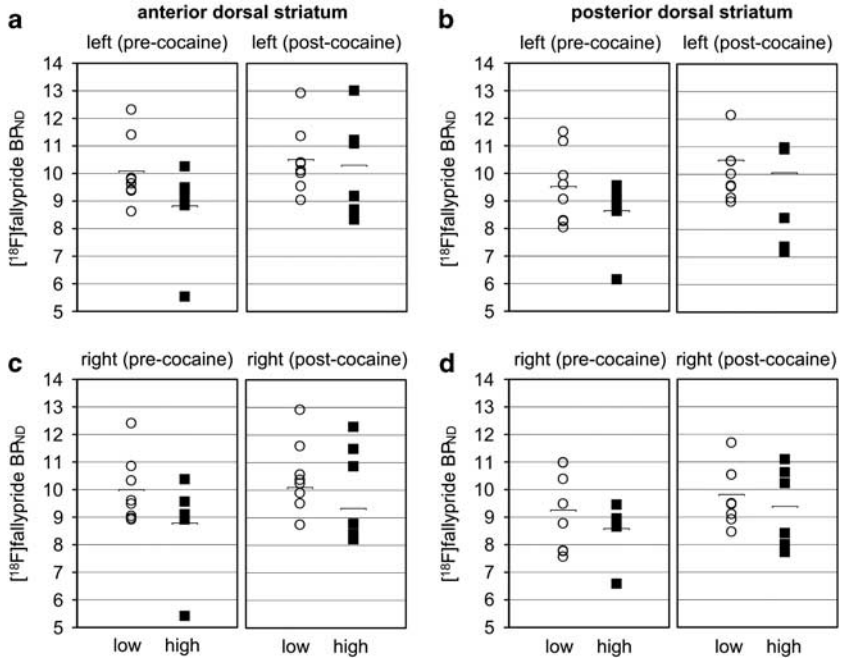

Figure 5 Binding potentials of [^{18}F]fallypride in the left (a, c) and right (b, d) anterior and posterior dorsal striatum of LI (square symbols, $n = 8$) and HI (circle symbols, $n = 6$) rats before ('pre-cocaine') and after ('post-cocaine') cocaine self-administration. There were no significant baseline differences in [^{18}F]fallypride BP_{ND} in either brain region between LI and HI rats. Prior cocaine exposure also had no significant effect on [^{18}F]fallypride BP_{ND} in the anterior and posterior dorsal striatum of LI and HI rats.

$D_{2/3}$ receptor availability evident during withdrawal from cocaine were regionally-indiscriminate and probably therefore mediated by common global underlying mechanisms rather than by mechanisms that were specific to the ventral striatum. In considering the nature of this mechanism, it is unlikely that aging had any major bearing on these results (ie, the time elapsed between the first and second PET scan) since aging studies in both human and non-human subjects invariably report a decrease in $D_{2/3}$ receptors in the striatum (Giardino, 1996; Morris *et al*, 1999; Volkow *et al*, 1996; Wong *et al*, 1984), not an increase as found in the present study.

Several explanations are possible to account for the observed increase in $D_{2/3}$ receptor availability in the dorsal and ventral striatum of rats exposed to cocaine. Firstly, a consistent effect associated with cocaine withdrawal is an upregulation of striatal D_3 receptors (Conrad *et al*, 2010; Neisewander *et al*, 2004). As [^{18}F]fallypride binds to both D_2 and D_3 receptors (Mukherjee *et al*, 1995) it is possible that the cocaine-induced increase in [^{18}F]fallypride BP_{ND} was caused by a selective upregulation of D_3 receptors. Indeed, binding of the radiotracer [^{11}C]-(+)-PHNO, which has preferential affinity for D_3 receptors, is reportedly increased in the striatum of methamphetamine poly-drug users (Boileau *et al*, 2012). However, it is unclear whether the low expression of D_3 receptors in the dorsal striatum compared with the ventral striatum (Sokoloff *et al*, 1990) would be sufficient to generate the broadly similar increases in [^{18}F]fallypride BP_{ND} observed in both striatal regions in the present study. Secondly, withdrawal from stimulant drugs (<3 weeks) is associated with behavioral sensitization to direct-acting D_2 receptor agonists (De Vries *et al*, 2002; Edwards *et al*, 2007; Robinson and Berridge, 2008; Ujike *et al*, 1990). This effect may reflect the reported increase in high-affinity D_2 receptors in the striatum of rats withdrawn from cocaine self-administration (Briand *et al*, 2008). However, as fallypride is unlikely to distinguish between low- and high-affinity D_2 receptor states (Seeman *et al*, 2003) this mechanism would appear unlikely in the present context. Thirdly, the observed increase in [^{18}F]fallypride BP_{ND} in rats withdrawn from cocaine may reflect a reduction in DA release in the striatum.

Although post-mortem and imaging studies evaluating the dopamine transporter (DAT) in chronic cocaine abusers have been mixed and inconclusive, there has been no compelling evidence that this presynaptic marker is downregulated in cocaine addiction, putatively caused by a loss of dopaminergic terminals and/or a change in the regulation of this primary protein target (Narendran and Martinez, 2008). It is probable therefore that the downregulation of $D_{2/3}$ receptors in the striatum of abstinent cocaine addicts (Martinez *et al*, 2004; Volkow *et al*, 2003) and in animals (Nader *et al*, 2006) reflects a compensatory response of post-synaptic $D_{2/3}$ receptors to limit the effects of repeated drug-induced increases in DA release in this region. On the basis of the present findings this may be the predominant effect when the baseline pool of $D_{2/3}$ receptors in the striatum is high. By contrast, and in keeping with a recent study in humans expressing high levels of impulsivity and low $D_{2/3}$ receptor availability in the midbrain (Buckholtz *et al*, 2010), an adaptive consequence of prior cocaine exposure may be to preferentially increase the availability of presynaptic $D_{2/3}$ receptors in the striatum when their density at baseline is low. If this hypothesis is correct, the present results suggest the novel inference that compensatory changes in presynaptic DA receptors are more likely

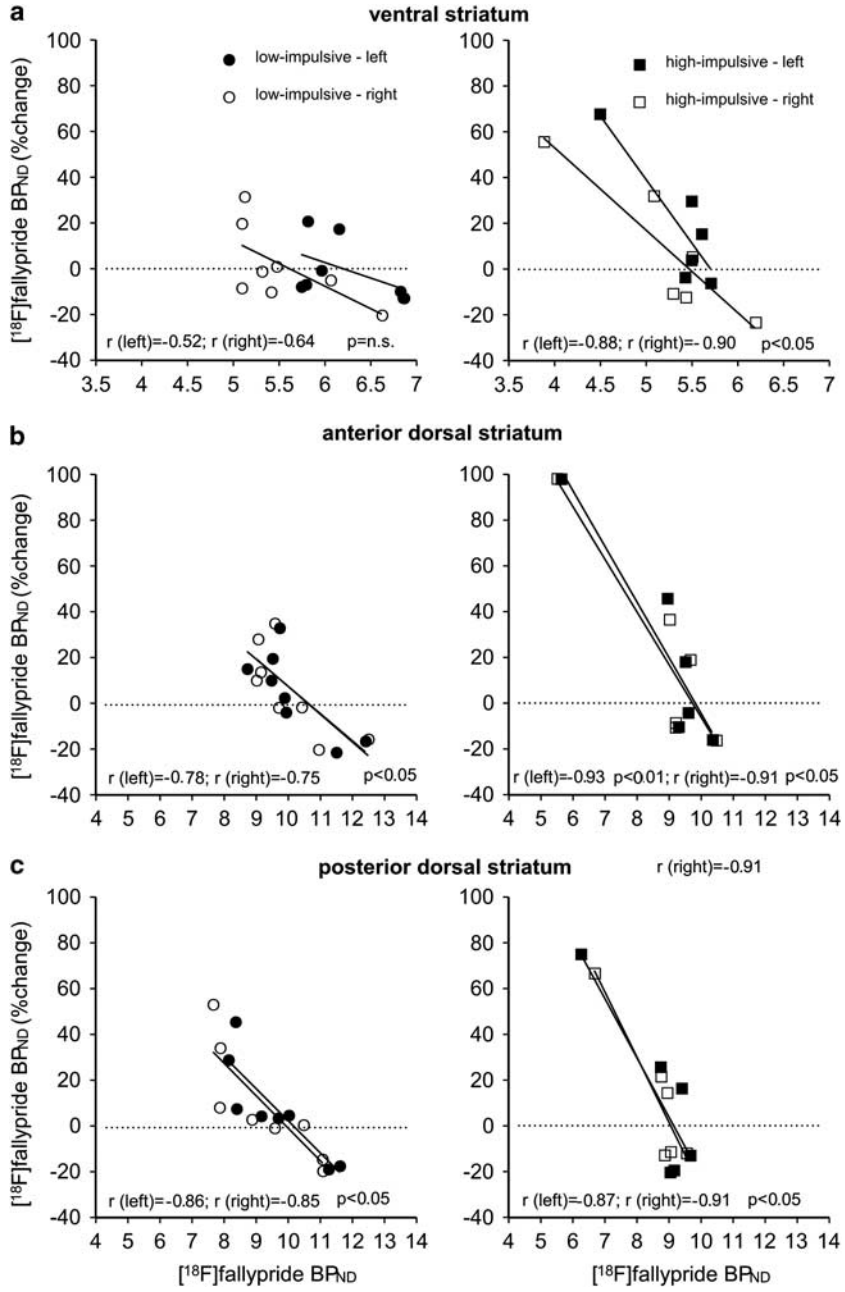

Figure 6 Relationship between the percentage change in [^{18}F]fallypride BP_{ND} in ventral and dorsal striatum before and after the exposure of LI and HI rats to cocaine as a function of baseline (ie, pre-cocaine) [^{18}F]fallypride BP_{ND}. With the exception of [^{18}F]fallypride BP_{ND} in the ventral striatum of LI rats, the results show that the effects of cocaine on $D_{2/3}$ receptor availability depend in an inverse manner on baseline [^{18}F]fallypride BP_{ND}. The horizontal dotted line depicts no net effect of cocaine on [^{18}F]fallypride BP_{ND}. Pearson product moment correlation coefficients and *P*-values are given in each panel.

when baseline $D_{2/3}$ receptor availability is relatively low in the striatum.

Response-Contingent Cocaine Administration Has Persistent Effects on the Expression of Impulsive Behavior

Exposure of HI rats to cocaine had the dramatic effect of reducing their impulsive behavior on the five-choice task when subsequently tested 2 weeks after the last drug self-administration session. In addition, the accuracy of HI rats was no longer significantly different from LI rats when tested in withdrawal. We believe that these effects were caused by the exposure of rats to cocaine itself, and subsequent withdrawal, as a separate group of age-matched but drug-naive high-impulsive rats continued to show high levels of impulsivity on this task at an identical time of testing. Consistent with this conclusion, we have shown that yoked intravenous infusions of saline over several weeks have no effect on impulsive behavior (Dalley *et al*, 2007a; Dalley *et al*, 2005a). In addition, the normalizing effect of prior cocaine exposure on impulsivity was not due to

differences in the quantity or rate of cocaine self-administration, which was not different between LI and HI rats. The failure to observe differential rates of cocaine escalation between the impulsivity groups, as reported previously (Dalley *et al*, 2007a), may be due to the continuous daily exposure of rats to cocaine self-administration in the present study, unlike our earlier study, which repeatedly exposed rats to cycles of cocaine self-administration and periods of forced withdrawal in between to assess longitudinal effects on impulsivity. Nevertheless, two high-impulsive rats in the present study developed excessive rates of cocaine self-administration with subsequent adverse health effects that led to their removal from the study. The exclusion of these animals may have influenced the conclusion of no difference in escalation between the two impulsivity groups.

The reduction in impulsivity in HI rats induced by prior cocaine exposure was behaviorally-selective with no ancillary effects on the speed or motivation to respond on the task. The neural basis of reduced impulsivity in cocaine-exposed rats remains unclear but converging evidence implicates a correction of $D_{2/3}$ receptor-mediated neurotransmission in the nucleus accumbens, a key region involved in regulating impulse control (Basar *et al*, 2010; Dalley *et al*, 2011). In a recent autoradiography study, $D_{2/3}$ receptors were found to be significantly reduced in the nucleus accumbens shell, but not core, of drug-naive HI rats (Jupp *et al*, 2013). Consistent with this evidence, impulsivity was exacerbated in HI rats following local infusions of a $D_{2/3}$ receptor antagonist in the shell (Besson *et al*, 2010). Thus, our present PET findings suggest that cocaine pre-exposure may attenuate impulsivity in HI rats by producing a long-lasting upregulation of $D_{2/3}$ receptors in the shell subregion of the nucleus accumbens. This putative mechanism appears to be restricted to HI rats because withdrawal from cocaine had no significant effect of impulsivity in LI rats. Moreover, in LI rats, cocaine did not alter $D_{2/3}$ receptor availability in the ventral striatum.

Clinical Implications

Deficiencies in behavioral inhibition are present in neuropsychiatric disorders such as ADHD and addiction, and are associated with DA dysfunction (Koob *et al*, 2010; Monterosso *et al*, 2005; Swanson *et al*, 2007). Here we show that impaired inhibition in a rodent test of impulsivity is allied to a relative deficiency in $D_{2/3}$ receptor availability in the ventral striatum, and that prior response-contingent exposure to cocaine both restores $D_{2/3}$ receptor availability in this region and improves impulse control. These findings accord with reports that $D_{2/3}$ receptor agonists improve response inhibitory control in stimulant addicts (Ersche *et al*, 2011) and that individual variation in $D_{2/3}$ receptors predicts inhibitory control deficits in methamphetamine-treated monkeys (Groman *et al*, 2012). Our results are also broadly compatible with the rate-dependency hypothesis of stimulant drug action in ADHD, postulated to depend on baseline differences in behavior (Dews and Wenger, 1977; Robbins and Sahakian, 1979). In this study, we demonstrate evidence for baseline dependency at the neurobiological level in the striatum and this may be relevant to recent findings of reduced $D_{2/3}$ receptor availability in the nucleus accumbens and caudate nucleus of unmedicated adults with ADHD (Volkow *et al*, 2009), as well as evidence that treatment response in this disorder is associated with increased DA transmission in the ventral striatum (Volkow *et al*, 2012). Thus, the clinical efficacy of stimulant drugs such as methylphenidate in ADHD may depend, in part, on restoring $D_{2/3}$ receptor signalling in the ventral striatum of impulsive individuals.

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DISCLOSURE

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