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ORIGINAL INVESTIGATION

# The self-administration of rapidly delivered cocaine promotes increased motivation to take the drug: contributions of prior levels of operant responding and cocaine intake

**Karim Bouayad-Gervais · Ellie-Anna Minogianis · Daniel Lévesque · Anne-Noël Samaha**

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**Abstract**
*Rationale* Rapid drug delivery to the brain might increase the risk for developing addiction. In rats, increasing the speed of intravenous cocaine delivery (5 vs. 90 s) increases drug intake and the subsequent motivation to self-administer cocaine. Increased motivation for cocaine could result not only from more extensive prior drug intake and operant responding for drug, but also from neuroplasticity evoked by rapid drug uptake.
*Objective* We determined the contributions of prior drug intake and operant responding to the increased motivation for cocaine evoked by rapid delivery. We also investigated the effects of cocaine delivery speed on corticostriatal expression of brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB) mRNA.
*Methods* Rats self-administered cocaine (0.25 mg/kg/infusion) delivered over 5 or 90 s during short-access (1 h/session; ShA) or long-access (6 h; LgA) sessions. Motivation for cocaine was then assessed by measuring responding under a progressive ratio schedule of reinforcement. Next, BDNF and TrkB mRNA levels were measured in 5- and 90-s rats.
*Results* Five-second ShA and 5-s-LgA rats were more motivated for cocaine than their 90-s counterparts. This effect was dissociable from previous levels of drug intake or of operant responding for cocaine. In parallel, only rats self-administering rapid cocaine injections had altered BDNF and TrkB mRNA levels in corticostriatal regions.
*Conclusions* Rapid drug delivery augments the motivation for cocaine independently of effects on the levels of drug intake or operant responding for drug. We suggest that rapid delivery might increase the motivation for drug by promoting neuroplasticity within reward pathways. This neuroplasticity could involve increased regulation of BDNF/TrkB.

**Keywords** Addiction · Cocaine · Progressive ratio · Intravenous self-administration · Speed of drug delivery · Operant responding · BDNF · TrkB

## Introduction

The faster a drug of abuse reaches the brain, the greater is the risk of developing addiction. For example, routes of cocaine administration that result in a rapid onset of drug effects (e.g. smoking or intravenous (i.v.) injection vs. the intranasal route) are associated with a greater loss of control over cocaine intake (Gawin and Ellinwood 1988), greater abuse liability, greater propensity for drug addiction (Chen and Anthony 2004; Gossop et al. 1994; Hatsukami and Fischman 1996; O'Brien and Anthony 2005) and a more rapid progression of addiction (Gorelick 1992).

Addiction is more likely and more severe when drugs reach the brain rapidly, but it is not known why. Animal studies have investigated the influence of the speed of drug onset on the neurobehavioural impact of drugs by varying the speed of i.v. drug delivery between 5 and 100 s. These injection speeds produce different magnitudes of subjective drug effects in humans (Abreu et al. 2001), approximate the different rates of rise of plasma cocaine levels when the drug is smoked

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versus snorted (Jones 1990), but would hold peak brain levels of cocaine, dopamine and dopamine transporter blockade constant in laboratory animals (while producing different *rates of rise* of all three measures (Ferrario et al. 2008; Samaha et al. 2002; Woolverton and Wang 2004). Increasing the speed of drug delivery across this range promotes the development of psychomotor sensitization (Samaha et al. 2002; Samaha et al. 2004; Samaha et al. 2005), increases cocaine intake and produces a more persistent vulnerability to relapse (Wakabayashi et al. 2010). In addition, a key behavioural symptom of addiction is increased motivation for drug that is reflected by the continued pursuit of drug in the face of rising costs and adverse consequences (Gawin 1991; Kalivas and Volkow 2005; Robinson and Berridge 1993). Our recent work shows that rats self-administering rapid (5 s) versus slower (90 s) cocaine injections take significantly more drug and are later more motivated to self-administer cocaine, as measured by responding for the drug under a progressive ratio (PR) schedule of reinforcement [(Minogianis et al. 2013) see also (Liu et al. 2005b)]. This is consistent with recent work by Zimmer et al. (2012) showing that rapidly spiking brain levels of cocaine (achieved by giving intermittent access to the drug during 6-h self-administration sessions) lead to much greater motivation to take the drug than high, sustained brain levels (achieved by giving continuous drug access during 6-h sessions).

The question now is, how does rapidly delivered cocaine enhance the motivation to self-administer the drug? The available evidence shows that increasing the speed of i.v. cocaine delivery (5–45 vs. 90 s) leads to greater drug intake, followed by increased motivation to self-administer cocaine (Minogianis et al. 2013; Wakabayashi et al. 2010). Thus, one possibility is that the increased motivation for cocaine results from neuroplasticity induced by prior exposure to large amounts of the drug. This neuroplasticity could involve persistent changes to brain reward (Koob and Le Moal 1997) and decision-making (Jentsch and Taylor 1999) pathways and/or an expansion of the neural circuits engaged by cocaine to include networks that mediate obstinate stimulus-response habits (Everitt and Robbins 2013; Graybiel 2008; Leyton and Vezina 2013; Porrino et al. 2004). Second, enhanced motivation for cocaine could involve the enduring neuronal effects of prior extensive operant responding for the drug. Rats that self-administer rapid versus slower cocaine infusions show greater operant responding for cocaine during each self-administration session, thus acquiring more extensive operant training (Minogianis et al. 2013; Wakabayashi et al. 2010). Extensive operant responding for a reward can promote the transition from responding that is goal-directed to responding that is habit-based and inflexible, leading to increased reward seeking (Adams 1982; Adams and Dickinson 1981; Balleine and Dickinson 1998; Colwill and Rescorla 1985; Everitt and Robbins 2005). In the context of drug self-administration, a high level of operant responding for cocaine has been shown to predict a high level of cocaine-induced reinstatement (Keiflin et al. 2008). Third, rapid drug delivery could enhance the motivation for cocaine by promoting changes within brain reward and incentive motivation circuits. For example, the faster drugs like cocaine or nicotine reach the brain, the more readily they activate mesocorticolimbic regions, as measured by indices such as immediate early gene regulation (Samaha et al. 2004; Samaha et al. 2005), heat-producing metabolic activity (Brown and Kiyatkin 2005) and glucose utilization (Porrino 1993). In addition, 'spiking' rather than sustained brain levels of cocaine enhance cocaine's potency in inhibiting the dopamine transporter in the nucleus accumbens (Calipari et al. 2013)—an action that is critical to cocaine's reinforcing effects.

Cocaine and related drugs evoke many cellular and molecular changes within brain reward and motivation circuits. Amongst those changes that have been shown to directly modulate drug use are alterations in the expression of the neurotrophin brain-derived neurotrophic factor (BDNF). In response to cell activity, BDNF is secreted (Matsumoto et al. 2008) and activates tropomyosin receptor kinase B (TrkB) receptors (Bibel and Barde 2000). This in turn modifies intracellular signalling and transcription factor activity (Lu 2003; Patapoutian and Reichardt 2001) to produce long-term changes in synaptic plasticity (McGinty et al. 2010). Chronic exposure to cocaine and other psychostimulant drugs alters brain BDNF mRNA and protein levels (Fumagalli et al. 2007; Grimm et al. 2003; Im et al. 2010; Meredith et al. 2002), and altered BDNF-mediated signalling specifically in midbrain and corticostriatal regions mediates drug-seeking and drug-taking behaviours (Graham et al. 2007; Graham et al. 2009; Im et al. 2010; McGinty et al. 2010). Thus, our objectives were twofold. First, we sought to determine the contributions of prior level of drug intake and extent of operant responding for drug to the increased motivation to self-administer cocaine evoked by rapid drug delivery. Second, we wished to determine how variations in the speed of cocaine delivery alter the expression of BDNF and TrkB mRNA within corticostriatal regions.

## Materials and methods

*Subjects and housing* Male Wistar rats (Charles River Laboratories, St-Constant, QC) weighing between 200–250 g upon arrival were housed individually on a 12 h/12 h dark/light cycle (lights off at 8:00 a.m.). Experiments were conducted during the dark phase of the rats' circadian cycle. Water was available ad libitum. Except where noted, food was restricted to 25 g of standard rat food chow per day. The animal ethics committee of the Université de Montréal approved all procedures.

*Self-administration apparatus* Self-administration training and testing occurred in standard operant conditioning chambers (MED Associates Inc.; St Albans. VT, USA), as described in Samaha et al. (2011). Infusion pumps with 3.33 RPM motors were used to deliver cocaine over 5 or 10 s, and infusion pumps with 0.1 RPM motors were used to deliver the drug over 90 s.

*Food training* Figure 1 illustrates the sequence of experimental events. Rats first underwent operant training with food as a reinforcer for 2 sessions (1 session/day). During each session, the house light was turned on and rats could press the left (active) lever to obtain a 45-mg, banana-flavoured food pellet (Grain-based Dustless Precision Pellets; Cedarlane Laboratories LTD, Burlington, ON) under a fixed ratio 1 (FR1) schedule of reinforcement. Pressing on the right (inactive) lever had no programmed consequences. Sessions ended after a maximum of 100 pellets or 30 min. Animals that failed to acquire the task after two sessions were given an overnight training session. During food training, animals received 15 g of standard rat food chow in their home cage.

*Catheter implantation and cocaine self-administration training* Under isoflurane anaesthesia, rats were implanted with custom-made, chronic indwelling catheters into the jugular vein, as described in Samaha et al. (2011). From then on, catheters were flushed with 0.1 ml of saline or 0.1 ml of saline containing 0.2 mg/ml of heparin (Sigma-Aldrich Inc., Oakville, ON), on alternate days. Following surgery, Baytril (enrofloxacin 10 mg/kg, CDMV, St-Hyacinthe, QC) was added to the rats' drinking water for 7–10 days to prevent post-surgery infections. Next, self-administration training was initiated in daily 1-h sessions. Rats were trained to press a lever for cocaine hydrochloride infusions (0.25 mg/kg/infusion; Medisca Pharmaceutique, Ville Saint-Laurent, QC) under an FR1 schedule of reinforcement, where each infusion was delivered over 5 s and was followed by a 20-s timeout period. Once rats met minimum training criteria (≥5 injections/session, taken at regular intervals) for 2 consecutive days, the response requirement was increased to FR2. Once training criteria were met again, the timeout was extended to 65 s and finally to 85 s. An 85-s timeout period ensured that the projected experimental groups (rats self-administering cocaine infusions over 5 vs. 90 s) had access to the same number of infusions during each session. The average number of injections/session over the last 2 training days was 16.6± 0.8 (SEM).

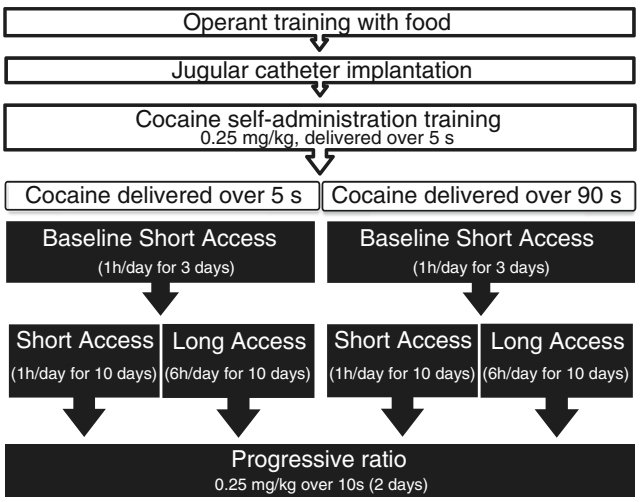


**Fig. 1** Timeline of experimental events. *h* hour, *s* second

## Experiment 1. The contributions of level of drug intake and operant responding for cocaine

*Cocaine self-administration under short- and long-access conditions* After cocaine self-administration training, rats were assigned to one of two groups such that average drug intake, extent of operant responding (i.e. number of active lever presses performed to obtain cocaine), days spent in training and number of inactive lever presses on the last 2 days of training were comparable across groups. For 3 sessions, one group self-administered cocaine infusions delivered over 5 s with an 85-s timeout period and the other group self-administered infusions delivered over 90 s with no timeout. Sessions lasted for 1 h (short access (ShA); referred to as 'baseline short access' in Fig. 1). For the next 10 sessions, each group was further divided in two and allowed to self-administer cocaine during either short (1 h)- or long (6 h)-access sessions (ShA and LgA, respectively). Thus, four groups were generated; 5s-ShA, 90s-ShA, 5s-LgA and 90s-LgA. Based on prior work (Crombag et al. 2008; Liu et al. 2005b; Minogianis et al. 2013; Wakabayashi 2010), we predicted that during ShA sessions, drug intake and the level of operant responding for drug would not differ between the 5- and 90-s groups. This would provide two groups that differed only in the speed of the cocaine injections they self-administered. Following 10 ShA or LgA sessions, rats remained in their home cages for 4–5 days. During this period and again at the end of the experiment, catheter patency was assessed by intravenous infusion of a sodium thiopental/sterile water solution (0.2 ml of a 20 mg/ml solution, Vétoquinol, Lavaltrie, QC). Rats that failed to become ataxic within 5 s were removed from the study.

*Cocaine self-administration under a progressive ratio schedule of reinforcement* For the next 2 days, the motivation for cocaine was measured using a PR schedule of reinforcement (1 session/day). The number of lever presses required to obtain cocaine increased exponentially with each successive infusion (response ratio$=[5e^{(\text{injection number}\times 0.2)}]-5$) (Richardson and Roberts 1996). Sessions ended after a maximum of 5 h or when an hour elapsed since the last infusion. The number of infusions earned prior to this point was used as

an index of the motivation for cocaine. Cocaine infusions (0.25 mg/kg/infusion) were delivered over 10 s to all rats. All of the rats in experiments 1 and 2 attained their breakpoint prior to the 5-h limit.

Experiment 2. The influence of the speed of cocaine delivery on the expression of BDNF and TrkB mRNAs

In a separate set of rats, we examined the influence of the speed of cocaine delivery on BDNF and TrkB mRNA expression within corticostriatal regions. Extended periods of drug taking are thought to be a prerequisite for the emergence of addiction-relevant changes in the brain (Ahmed and Koob 1998; Belin et al. 2009; Deroche-Gamonet et al. 2004; Vanderschuren and Everitt 2004). As such, we gave all animals extended daily access to cocaine (LgA) in this experiment.

*Cocaine self-administration* To shorten the length of the total training period, animals did not receive food training. The remainder of the training and testing procedures were as described in experiment 1, unless noted otherwise. Rats were assigned to one of two groups; a control group allowed to self-administer saline and a group allowed to self-administer cocaine, both delivered over 5 s. Following self-administration training as described above, cocaine-taking rats were assigned to the 5s-LgA or 90s-LgA groups; saline rats were assigned to self-administer saline delivered over 5 or 90 s. All animals including the saline controls were then given a total of nine LgA sessions and were also tested under PR as described above, for a total of four sessions. Finally, the animals were given one last self-administration session (FR1 for 1 h) and sacrificed 15 min later. Following an injection of cocaine, BDNF mRNA levels peak between 1 and 2 h post injection [though some expression can be seen 0.5 h post injection (Fumagalli et al. 2007; Graham et al. 2007; Le Foll et al. 2005)]. The 15-min time point was chosen to ensure that the 5s- and 90s-LgA groups had taken a sufficient number of cocaine infusions prior to sacrifice. Brains were extracted, plunged into isopentane (−50 °C) for 7 s and stored at −80 °C until processing.

*In situ hybridization* BDNF or TrkB mRNA expression was labelled on 12-μm-thick coronal brain sections using a [$^{35}$S]-UTP-labelled riboprobe complementary to BDNF or TrkB, respectively, using procedures described in Bedard et al. (2011). The complementary RNA (cRNA) probe for TrkB stems from a 284-bp (nucleotide 2597–2880, NM_008745) EcoRI–BamHI fragment of a full-length mouse TrkB cDNA subcloned into pGEM-4Z and linearized with Kpn I. The cDNA of BDNF was subcloned into pCR 2.1 and linearized with Xho I and corresponds to a 284-bp (nucleotide 99–448, NM_007540) fragment. Both cRNA probes were synthesized and labelled using a Promega riboprobe kit, [35S]UTP and the RNA polymerase Sp6. Brain sections were then placed against X-ray film (Kodak Biomax-MR; VWR, Town of Mount-Royal, QC) for either 9 (BDNF) or 4 (TrkB)days. An experimenter blind to condition quantified mRNAs on autoradiographs by translating optical grey densities into microcuries per gram of tissue using a $^{14}$C standard curve (ARC-146A, American Radiolabeled Chemicals, St-Louis, MI) and Image J software (NIH, Bethesda, MD). Background values were obtained from the rhinal fissure (+3.4 mm relative to Bregma) or the corpus callosum (+2.6 to 0.0 mm relative to Bregma) of each section and were subtracted from analysis. BDNF and TrkB mRNA values were measured in the ventrolateral (VLO) and lateral (LO) orbitofrontal cortex, the cingulate (Cg1/Cg2 aspects; CG), medial prefrontal (prelimbic and infralimbic aspects), frontal (FR1/FR2) and parietal (PAR1) cortices, as well as in the nucleus accumbens core and shell and the dorsomedial (DM), dorsolateral (DL), ventromedial (VM) and ventrolateral (VL) quadrants of the caudate-putamen. For each brain region, mRNA levels were averaged over 2–5 sections/rat. Anatomical regions were identified according to (Paxinos and Watson 1986).

*Statistics* Repeated measures two-way ANOVA was used to analyse the influence of injection speed (5 or 90 s) and session length (ShA or LgA) on the number of self-administered infusions during ShA or LgA sessions. Mauchly's test is reported in cases where the sphericity assumption is violated. In such cases, degrees of freedom were corrected using the Greenhouse–Geisser estimate of sphericity (ε). Significant group x session interaction effects were analysed further using a simple contrast with the first session as reference. Cumulative cocaine intake was calculated as milligrams of cocaine consumed per kilogram across all self-administration sessions, including acquisition sessions. Cumulative active lever presses for cocaine were also summed across all self-administration sessions including acquisition sessions. Each measure was analysed using two-way ANOVA. Significant group effects were analysed further using the Bonferonni post hoc test. Based on our prior work (Minogianis et al. 2013), an a priori prediction was made that the 5-s rats would take more cocaine under progressive ratio than the 90-s rats. Thus, number of infusions taken during PR sessions was analysed using a one-tailed unpaired *t* test for the ShA and LgA groups. Pearson *R* correlation was used for all correlations. In experiment 2, number of infusions prior to sacrifice was analysed using a two-tailed unpaired *t* test. BDNF and TrkB mRNA levels were analysed using one-way ANOVA followed by Tukey's multiple comparison test. A *p* value below 0.05 was considered significant.

## Results

Experiment 1. The contributions of level of drug intake and operant responding for cocaine

*Cocaine self-administration under short- and long-access conditions* Figure 2 illustrates the average number of self-administered cocaine infusions as a function of the speed of cocaine delivery and the length of the self-administration sessions. During the first three ShA sessions [first three sessions in (a) and inset in (b)], the speed of cocaine delivery had no effect on the number of self-administered infusions ($p>0.05$). However, past these initial 3 sessions, rapid i.v. cocaine injections (delivered over 5 vs. 90 s) led to greater drug intake, both in rats given ShA (Fig. 2a) and LgA (Fig. 2b, c) sessions (a, sessions 4–13, $F(1, 24)=13.32$; b, sessions 1–10, $F(1, 23)=24.78$; c, sessions 1–10, $F(1, 23)=30.60$; all $P$s $<0.01$). In addition, under LgA conditions, the self-administration of rapid, but not slower cocaine injections led to an escalation in drug intake over time, both when considering intake during the first hour and total intake during the 6-h session (group x time interaction; b, Mauchly's test ($X^2(44)=119.63$; $\varepsilon=0.46$), $F(4.11, 96.54)=4.67$; c, $F(9, 207)=4.91$; all $P$s $<0.05$). Additional post hoc comparisons revealed that in the 5s-LgA rats, escalation of intake in the first hour (Fig. 2b) began on the 6th LgA session, (as shown by greater drug intake relative to the first session), and persisted until the last (10th) session, and escalation of total intake during the 6-h session (Fig. 2c) began on the 2nd LgA session and persisted until the last (10th) session (all $P$s $<0.05$).

*Cumulative cocaine intake and extent of operant responding for cocaine* Figure 3 illustrates cumulative cocaine intake (a: the sum of all cocaine injections self-administered prior to progressive ratio testing multiplied by 0.25 mg/kg) and extent of operant responding for the drug (b: the sum of all active lever presses for cocaine prior to progressive ratio testing) in each experimental group. Increasing the speed of drug delivery increased both cumulative cocaine intake ($F(3, 47)=55.702$, $p<0.0001$) and extent of operant responding only in rats given LgA sessions ($F(3, 47)=29.165$, $p<0.0001$). The speed of drug delivery had no effect on either cumulative cocaine intake or extent of operant responding in the ShA groups (all $P$s $>0.05$). It should be noted that as shown in Fig. 2a, during some of the ShA sessions, the 5-s group took more cocaine than the 90-s group and thus also engaged in greater active lever pressing behaviour. However, during the preceding acquisition phase, cocaine intake and active lever presses were slightly greater in the 90-s versus 5-s rats (an observation that was not statistically significant). As a consequence, when cocaine intake or active lever presses are summed over all self-administration sessions prior to progressive ratio testing (acquisition+ShA sessions), there are no significant differences between the 5- and 90-s groups given ShA sessions.

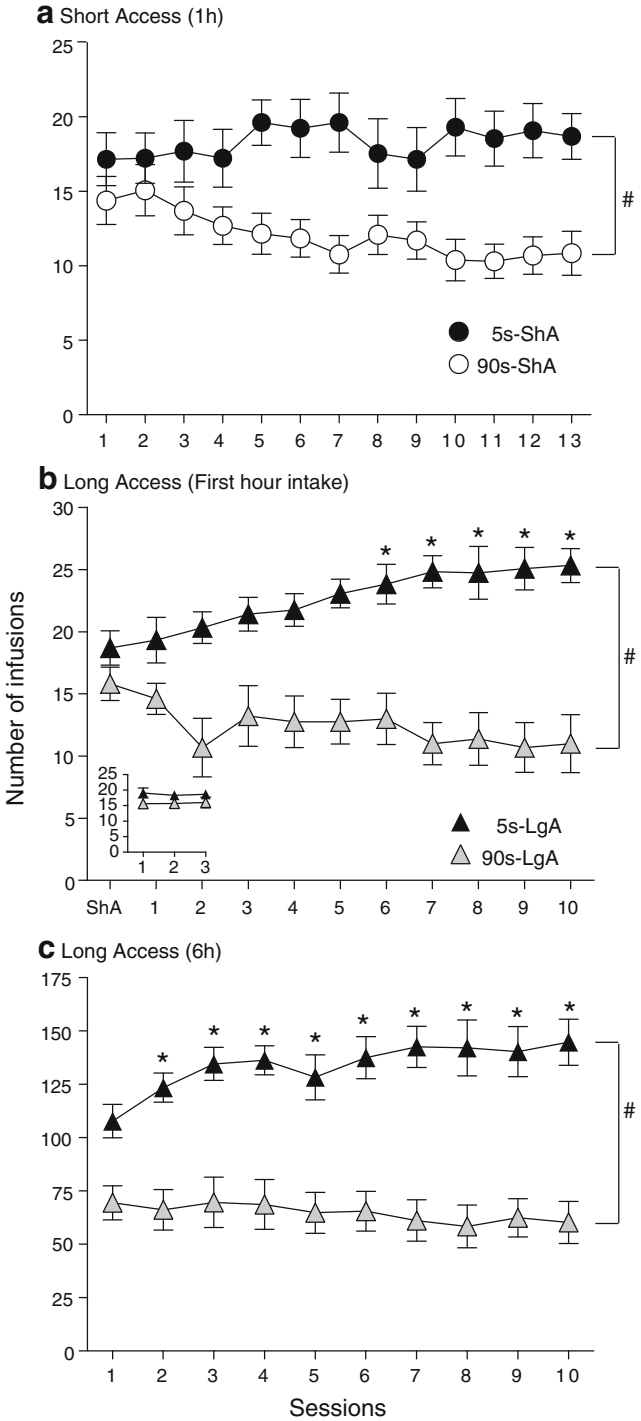


**Fig. 2** Rats self-administering intravenous cocaine infusions delivered over 5 versus 90 s take more drug during both ShA (**a**) and LgA (**b**, **c**) sessions. LgA rats received 3 ShA sessions prior to the 10 LgA sessions shown. The *inset* in (**b**) shows the average numbers of self-administered infusions during these three sessions. All values are mean ± SEM. $n=12$–13/condition. *s* second. *ShA* Short-Access sessions (1 h/day). *LgA* Long-Access sessions (6 h/day). $^{\#}p<0.05$ compared to the 90-s group. $^{*}p<0.05$ compared to the first LgA session in the 5-s group

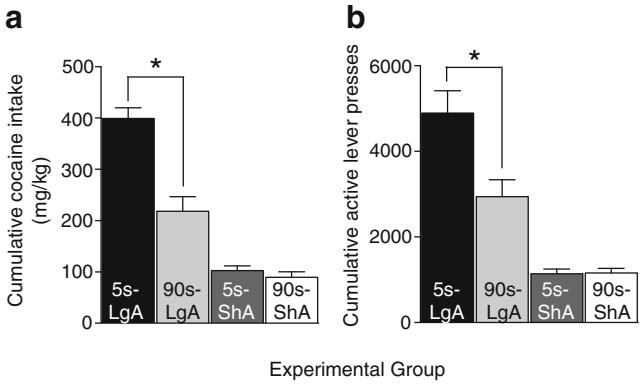


**Fig. 3** Increasing the speed of intravenous cocaine delivery increases cumulative cocaine intake (**a**) and extent of operant responding for cocaine (**b**) only in rats given LgA sessions. $n$=12–13/condition. *s* second. *ShA* Short-Access sessions (1 h/day). *LgA* Long-Access sessions (6 h/day). *$p$<0.05 compared to the 90-s-LgA group

*Cocaine self-administration under a progressive ratio schedule of reinforcement* As illustrated in Fig. 4, rats with a history of self-administering rapid cocaine injections during either LgA ($t$(23)=1.81; $p$<0.05) or ShA ($t$(24)=2.257; $p$<0.05) sessions take more drug under a progressive ratio schedule of reinforcement.

*Correlations between prior cumulative cocaine intake and number of infusions taken under progressive ratio* We performed correlations between average number of infusions earned across the two progressive ratio sessions on the one hand and prior, cumulative cocaine intake on the other. There was a significant correlation between these two variables only in the 90s-LgA group (data not shown; $r^2$=0.47, $p$<0.05). In this group, the greater the amount of cocaine consumed in the past, the greater the subsequent motivation to self-administer the drug. There were no significant correlations between these two variables in the other experimental groups (5s-LgA, $r^2$= 0.007; 5s-ShA, $r^2$=0.019; 90s-ShA, $r^2$=0.161; all *P*s >0.05).

*Correlations between extent of prior operant responding for cocaine and number of infusions taken under progressive ratio* We also performed correlations between average number of infusions earned across the two progressive ratio sessions on the one hand and prior, cumulative active lever presses for cocaine on the other. These two variables were significantly positively correlated in all groups (data not shown, 90s-LgA, $r^2$=0.406; 5s-ShA, $r^2$=0.391; 90s-ShA, $r^2$=0.377; all *P*s <0.05), except for the 5s-LgA group ($r^2$=0.028, $p$>0.05).

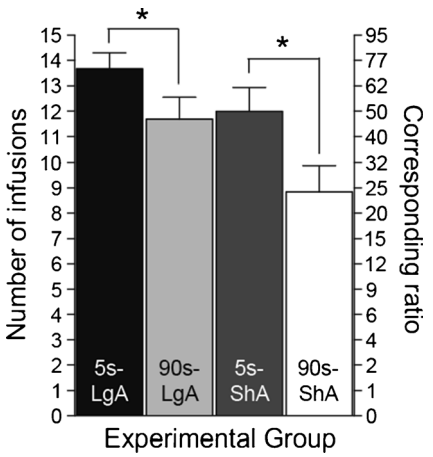


**Fig. 4** When tested under a progressive ratio schedule of reinforcement, rats that have previously self-administered intravenous cocaine infusions delivered over 5 versus 90 s take more of the drug. Corresponding ratios are shown for comparison. During progressive ratio testing, cocaine was injected over 10 s to all groups. All values are mean ± SEM. $n$=12–13/condition. *s* second. *ShA* Short-Access sessions (1 h/day). *LgA* Long-Access sessions (6 h/day). * $p$<0.05 compared to the corresponding 90-s group

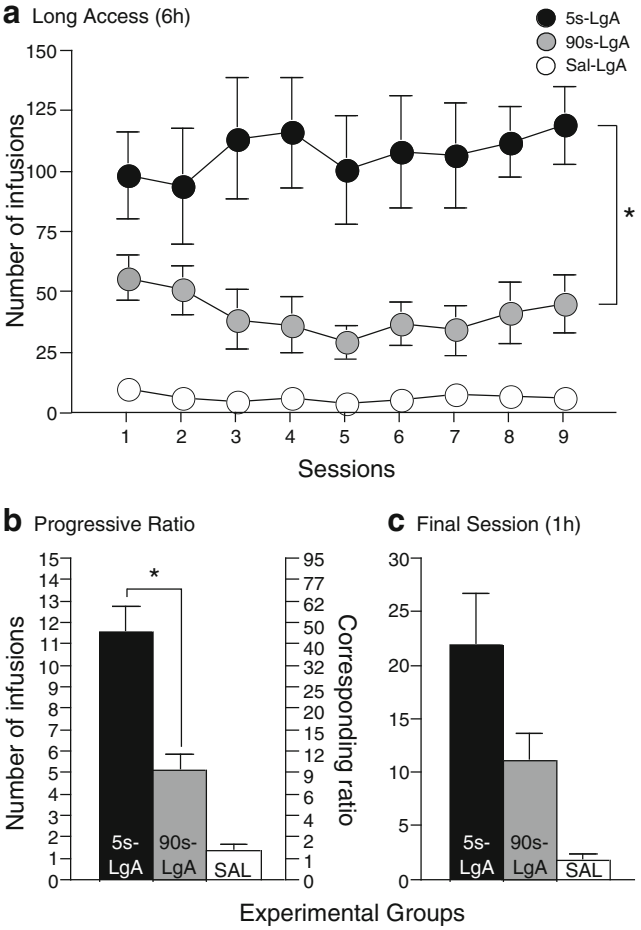


**Fig. 5** Self-administration data for the rats used to measure BDNF and TrkB mRNA levels. During long-access sessions, rats self-administering intravenous cocaine infusions delivered over 5 versus 90 s take more drug (**a**) and are subsequently more motivated to take cocaine as measured under progressive ratio (**b**). In the final self-administration session prior to brain collection (**c**), there was no statistically significant group difference in cocaine intake between the 5s- and 90s-LgA groups. All values are mean ± SEM. $n$=5–8/condition. *s* second. *LgA* Long-Access sessions (6 h/day). *$p$<0.05 compared to the 90-s group

Experiment 2. The influence of the speed of cocaine delivery on the expression of BDNF and TrkB mRNAs

There were no significant differences in either saline intake or BDNF and TrkB mRNA expression between the two saline groups (data not shown; all *P*s >0.05). Thus, these two groups were pooled into one (Sal-LgA). As in experiment 1, compared to rats in the 90s-LgA group, the 5s-LgA rats took a greater number of cocaine infusions both during the LgA sessions (Fig. 5a; F(1, 9)=9.90, $p$=0.01) and under progressive ratio conditions (Fig. 5b; $t$(9)=4.68; $p$=0.0006). This cohort of 5-s rats did not escalate their intake during LgA sessions. Doses of cocaine similar to the one used here do not always evoke escalated drug intake (Ferrario and Robinson 2007; Kippin et al. 2006; Mantsch et al. 2004). In the final self-administration session preceding brain collection, cocaine intake was not significantly different between the 5s- and 90s-LgA rats (Fig. 5c; $t$(9)=2.06; $p$=0.07), although visual inspection of Fig. 5c suggests a tendency.

Consistent with reports that the striatum does not synthesize reliably detectable levels of BDNF (Altar and DiStefano 1998), BDNF mRNA levels in the caudate-putamen and nucleus accumbens core and shell were notably low, with many animals having negative values. Thus, striatal BDNF mRNA levels were not analysed further. In the medial prefrontal cortex, there were no group differences in either BDNF or TrkB mRNA expression (data not shown; all *P*s >0.05). In the nucleus accumbens core and shell, there were no group differences in TrkB mRNA expression (data not shown; all *P*s >0.05).

Figure 6 illustrates BDNF and TrkB mRNA levels in the orbitofrontal cortex. In this cortical region, BDNF mRNA levels were greater in the 5s-LgA group compared to the 90s-LgA group (Fig. 6a, c; all *P*s <0.05), with no group differences in TrkB mRNA levels (Fig. 6b, d). Figure 7 shows BDNF and TrkB mRNA levels in the cingulate, frontal and parietal cortices. In the cingulate cortex, there were no group differences in BDNF mRNA expression (Fig. 7a; $p$>0.05), but TrkB mRNA levels were decreased in the 5s-LgA rats relative to both 90s-LgA and saline rats (Fig. 7b; all *P*s <0.05). In frontal and parietal cortices, the 5s-LgA rats had increased BDNF mRNA levels (Fig. 7c, e; all *P*s <0.01) and decreased TrkB mRNA levels (Fig. 7d, f; all *P*s <0.05), as compared to both 90s-

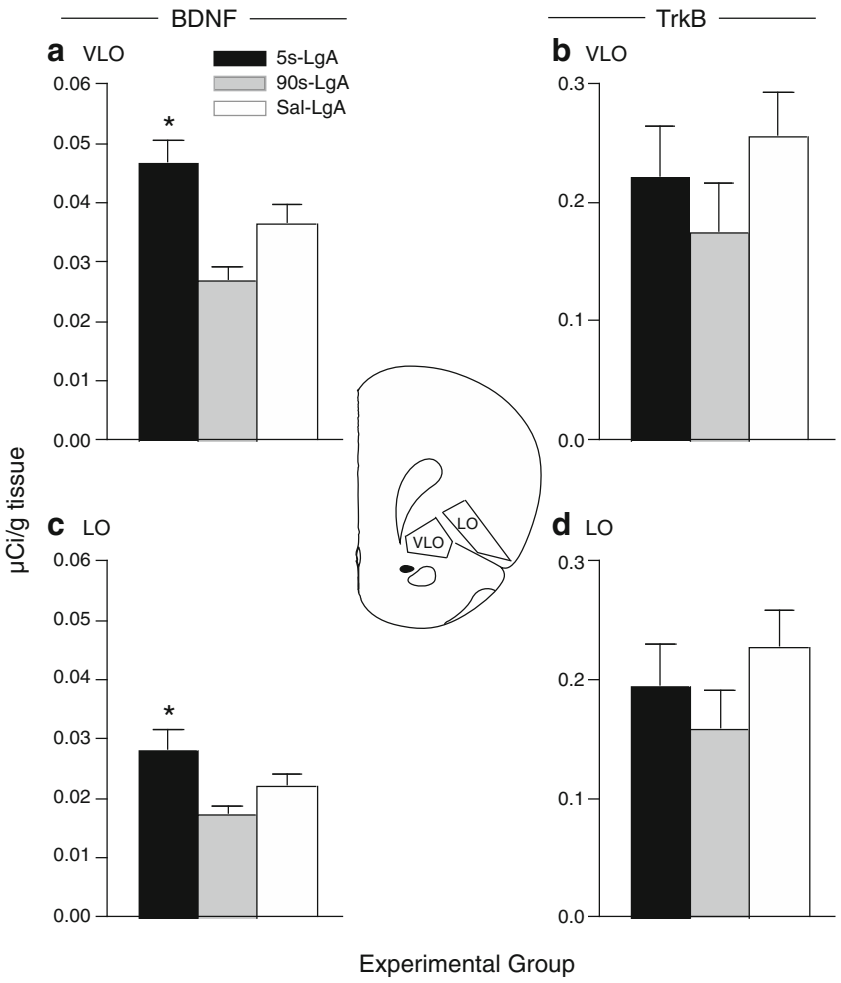


**Fig. 6** The self-administration of rapid cocaine injections increases BDNF mRNA levels in the orbitofrontal cortex (**a**, **c**) with no changes in TrkB mRNA levels (**b**, **d**). The figure shows brain-derived neurotrophic factor (BDNF) and tropomyosin-related kinase B (TrkB) mRNA levels in the ventrolateral (VLO; **a**, **b**) and lateral (LO; **c**, **d**) aspects of the orbitofrontal cortex. All values are mean ± SEM. $n$=5–8/condition. *s* second. *LgA* Long-Access sessions (6 h/day). *$p$<0.05 compared to the 90-s group

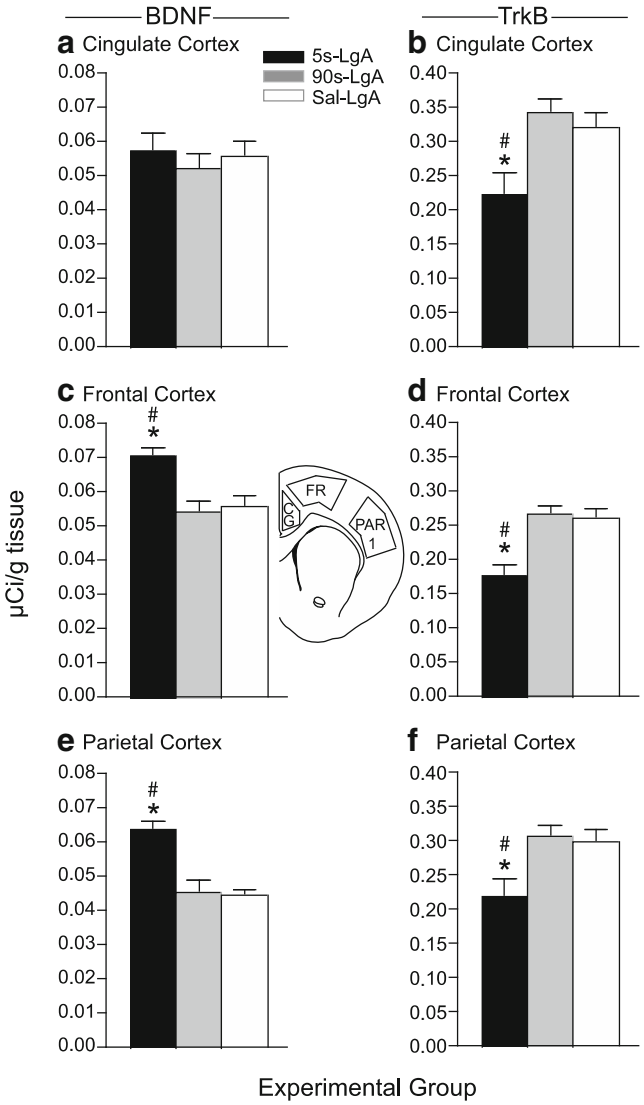


**Fig. 7** The effects of the speed of cocaine delivery on BDNF and TrkB mRNA levels in the cingulate (**a**, **b**), frontal (**c**, **d**) and parietal (**e**, **f**) cortices. All values are mean ± SEM. $n$=5–8/condition. *s* second. *LgA* Long-Access sessions (6 h/day). *CG* cingulate cortex, *FR* frontal cortex, *PAR1*, parietal cortex. *$p<0.05$ compared to the 90-s group. $^{\#}p<0.05$ compared to the saline (Sal-LgA) group

LgA and saline rats. Figure 8 shows TrkB mRNA data in the caudate-putamen. In all quadrants of the caudate-putamen, TrkB mRNA levels were decreased in the 5s-LgA rats (a, 5s-LgA<Sal-LgA; b and c, 5s-LgA<Sal-LgA and 90s-LgA; d, 5s-LgA<Sal-LgA; all *P*s <0.05). There were no other statistically significant differences.

Thus, in several cortical regions, rats that had self-administered rapid cocaine injections had increased BDNF mRNA levels and decreased TrkB mRNA levels. This was coupled with decreased TrkB mRNA expression within the caudate-putamen. In contrast, in all of the brain regions analysed, rats that had self-administered slow cocaine injections had levels of BDNF and TrkB mRNAs that were no different from control animals (all *P*s >0.05).

## Discussion

Our objectives were to (1) determine how the prior levels of cocaine intake and of operant responding for the drug contribute to the ability of rapid drug delivery to enhance the subsequent motivation to take cocaine and (2) determine how variations in the speed of cocaine delivery alter the expression of BDNF and TrkB mRNA within corticostriatal regions. The self-administration of rapidly delivered cocaine promoted greater drug intake and enhanced the subsequent motivation to self-administer the drug. This is consistent with our recent work showing that rats that have previously taken rapid cocaine infusions are more motivated to self-administer the drug in the future, across a range of doses (Minogianis et al. 2013). In the present study, the increased motivation for cocaine evoked by rapid drug delivery was not accounted for by effects on the prior levels of cocaine intake or of operant responding for the drug (the latter measured as the cumulative number of active lever presses performed to obtain cocaine prior to assessing the motivation for the drug). At the neurobiological level, the self-administration of cocaine altered BDNF and TrkB mRNA expression in corticostriatal regions *only* if the drug was delivered rapidly.

*The self-administration of rapidly delivered cocaine promotes increased drug intake* Rapid cocaine injections led to greater drug intake during both LgA and ShA sessions. This is in partial contrast with work showing that increasing the speed of i.v. cocaine delivery (5–100 s) increases drug intake during LgA, but not ShA sessions (Crombag et al. 2008; Minogianis et al. 2013; Wakabayashi et al. 2010). The discordance with the literature might be more apparent than real because prior studies did not test beyond 3–4 ShA sessions (Crombag et al. 2008; Minogianis et al. 2013; Wakabayashi et al. 2010). We also found that for the first four daily ShA sessions, there was no effect of the speed of i.v. delivery on cocaine intake (see Fig. 2). However, beyond these initial sessions, faster cocaine injections led to greater drug intake, suggesting an increase in cocaine's reinforcing efficacy with more chronic self-administration experience, even with limited daily access to the drug. This is reminiscent of reports showing that increasing the speed of i.v. cocaine or nicotine delivery does not alter the *acute* psychomotor activating effects of these drugs, but does promote the development of psychomotor sensitization following chronic drug exposure (Samaha et al. 2002; Samaha et al. 2004).

*Operant responding* Rapidly delivered cocaine enhanced the motivation for the drug and this was not simply predicted by prior, more extensive operant responding for cocaine (i.e. a greater cumulative number of active lever presses for the drug prior to progressive ratio testing). As an example, the 5- and 90-s rats given ShA sessions had similar histories of operant responding for cocaine, but the 5-s rats showed greater motivation for the drug. Similarly, the 90s-LgA group had access

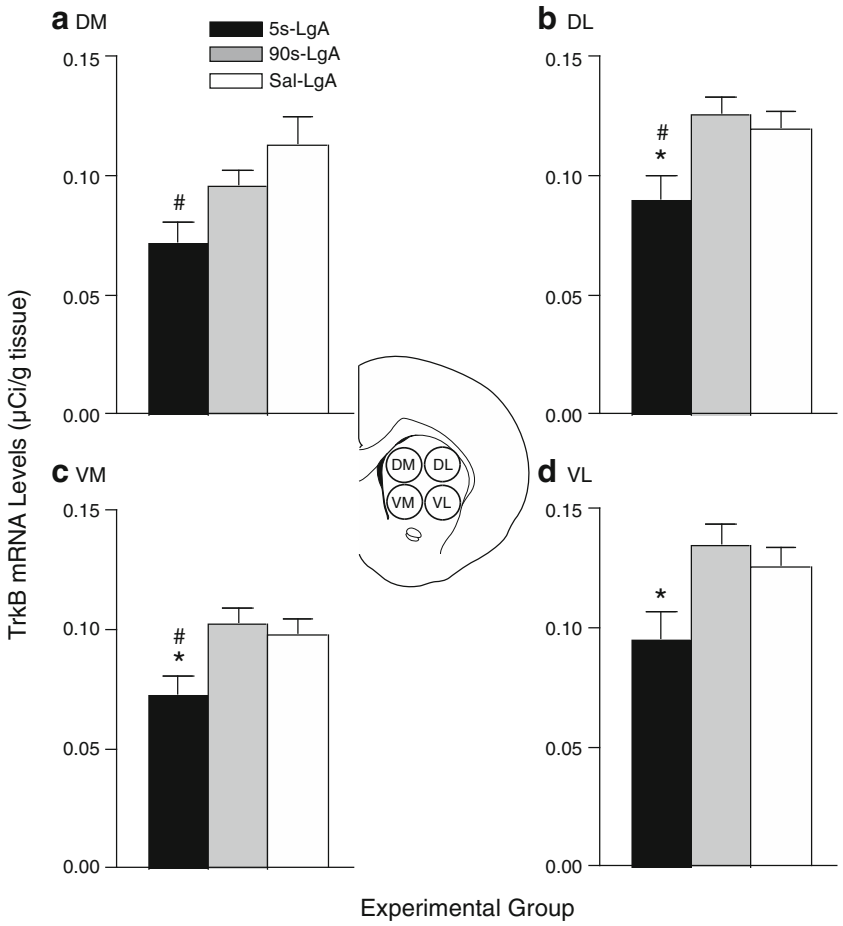


**Fig. 8** The self-administration of rapid cocaine injections decreases TrkB mRNA expression in the caudate-putamen. The figure shows TrkB mRNA levels in the dorsomedial (DM) (**a**), dorsolateral (DL) (**b**), ventromedial (VM) (**c**) and ventrolateral (VL) (**d**) aspects of the caudate-putamen. All values are mean ± SEM. $n$=5–8/condition. *s* second. *LgA* Long-Access sessions (6 h/day). *$p<0.05$ compared to the 90-s group. $^{\#}p<0.05$ compared to the saline (Sal-LgA) group

to cocaine 6 h/day and thus acquired a more extensive operant responding history than the 5s-ShA group (1 h/day), yet the two groups showed similar motivation for cocaine. Finally, there was no significant correlation between the extent of prior operant responding for cocaine and the motivation for the drug in 5s-LgA rats.

*Drug exposure* Increasing the speed of cocaine delivery increases drug intake [(Minogianis et al. 2013; Wakabayashi et al. 2010) and present findings], but this does not fully account for the ability of rapid drug delivery to enhance the subsequent motivation for cocaine. First, in rats given ShA sessions, total cocaine intake (taking into account both the acquisition and ShA testing phases) was similar in 5- and 90-s rats, yet the 5-s rats were subsequently more motivated to take cocaine. In addition, there was no significant correlation between prior cocaine intake and motivation for the drug in 5s-LgA animals. These observations are consistent with work showing that taking more cocaine in the past does not necessarily predict greater motivation to obtain the drug in the future (Morgan et al. 2006) and that differences in the motivation for cocaine can be observed between groups of rats with identical prior histories of drug intake (Minogianis et al. 2013). It is also noteworthy that rats given extended daily access to cocaine did not show greater motivation for the drug than rats given limited daily access. This is in accordance with some findings (Liu et al. 2005a; Oleson and Roberts 2009; Quadros and Miczek 2009) but not others (Hao et al. 2010; Paterson and Markou 2003; Ramoa et al. 2013; Wee et al. 2008). As has been discussed elsewhere (Oleson and Roberts 2009), the discrepancy could involve differences in rat strain, housing, PR ratio requirements and cocaine abstinence periods. As this issue unfolds, the present findings are in agreement with work showing that in predicting the motivation for cocaine, the decisive factor appears to be repeated and rapidly spiking brain levels of the drug, rather than high, stable brain levels of cocaine (Zimmer et al. 2012).

*Regulation of BDNF and TrkB mRNA expression* Our findings suggest that effects on the prior levels of cocaine intake or operant responding for cocaine cannot fully explain why the intake of rapidly delivered cocaine promotes increased motivation to self-administer the drug. A reasonable hypothesis is that exposure to rapidly delivered cocaine facilitates the neural plasticity that underlies enhanced motivation to obtain drug. This hypothesis is supported by empirical evidence. For example, increasing the speed of i.v. cocaine delivery (5–6 vs. 100–150 s) allows peak levels of striatal dopamine transporter

occupancy (Samaha et al. 2004; Woolverton and Wang 2004) and dopamine overflow (Ferrario et al. 2008) to be reached faster. In addition, the faster drugs like cocaine or nicotine reach the brain, the more readily they evoke cell activity within mesocorticolimbic regions (Brown and Kiyatkin 2005; Ferrario et al. 2008; Porrino 1993; Samaha et al. 2004; Samaha et al. 2005). Finally, rapidly spiking brain levels of cocaine promote sensitization to the neurochemical effects of cocaine at the dopamine transporter (Calipari et al. 2013).

The present results add to the previous literature by showing that cocaine alters BDNF and TrkB mRNA expression in corticostriatal structures *only* when it is delivered rapidly. When assessed immediately following a final self-administration session, 5-s rats had increased BDNF mRNA levels in several cortical regions, coupled with decreases in both cortical and caudate-putamen TrkB mRNA levels. This is consistent with evidence that cocaine alters BDNF and TrkB mRNA and protein levels in a time-dependent manner in several mesocorticolimbic structures (Fumagalli et al. 2007; Graham et al. 2007; Graham et al. 2009; Grimm et al. 2003; Im et al. 2010; Le Foll et al. 2005). In contrast, 90-s rats had normal levels of BDNF and TrkB mRNA in all regions analysed. Of note, increased BDNF mRNA was not always accompanied by a decrease in TrkB mRNA (see Figs. 6 and 7a, b), suggesting that changes in the transcription of one gene are not simply a compensatory response to changes in the transcription of the other. At this stage, we do not know if the observed changes in mRNA levels translate into protein changes, or how increased regulation of BDNF/TrkB mRNA expression might contribute to the ability of rapid drug delivery to enhance the motivation to self-administer cocaine. With these considerations in mind, a provocative finding here is that variations in the speed of cocaine delivery did not evoke diffuse and nonspecific changes in BDNF/TrkB transcription, but rather the effects were regionally specific. Thus, in specific brain regions (the caudate-putamen, orbitofrontal, frontal and parietal cortices, but not the nucleus accumbens or medial prefrontal cortex), BDNF/TrkB transcriptional processes are sensitive to small variations in the temporal dynamics of cocaine delivery. The effects of BDNF/TrkB-mediated signalling on cocaine taking and seeking are regionally specific (McGinty et al. 2010). Increased BDNF-mediated neurotransmission in the ventral midbrain, nucleus accumbens and caudate-putamen enhances drug use (Graham et al. 2007; Graham et al. 2009; Im et al. 2010; Li et al. 2013; Lu et al. 2004), while the same manipulation in the medial prefrontal cortex for example decreases cocaine-seeking behaviour (Berglind et al. 2007).

The largest effect of the speed of cocaine delivery on BDNF mRNA expression was found in the orbitofrontal cortex, where BDNF mRNA levels in the 5-s rats were nearly double those seen in 90-s rats. BDNF is synthesized and secreted in response to cell activity (Matsumoto et al. 2008). The self-administration of rapid cocaine injections increases the firing rate of orbitofrontal neurons (Guillem et al. 2010). Orbitofrontal neurons encode the motivational value of rewards (Tremblay and Schultz 1999; Wallis and Miller 2003) and send this information to the striatum to modulate goal-directed behaviour (Pennartz et al. 2000; Schultz et al. 2000). In this regard, it is of interest that BDNF synthesized in the orbitofrontal cortex (and other cortical areas) is transported to the caudate-putamen (Altar and DiStefano 1998; Gourley et al. 2013), where increased BDNF activity triggers increased drug-taking behaviour (Im et al. 2010). Thus, one can speculate that the rapid delivery of cocaine increases BDNF synthesis within the orbitofrontal cortex and other cortical areas, leading to increased BDNF-mediated signalling in the downstream caudate-putamen, and this in turn promotes increased drug intake and motivation to obtain cocaine. This hypothesis can be evaluated in the future by measuring and manipulating BDNF protein levels. In the mean time, we observed a decrease in TrkB mRNA levels within the caudate-putamen of rats that had self-administered rapid cocaine injections. Such a decrease would be expected in the presence of excess BDNF-mediated signalling.

In summary, independent of any effects on the extent of drug intake or operant responding for cocaine, increasing the speed of drug delivery augments the motivation to obtain cocaine. At the neurobiological level, this is potentially linked to increased regulation of BDNF and TrkB mRNA in corticostriatal nuclei. Our findings add to an emerging literature suggesting that the intake of cocaine under conditions that lead to a rapid rise in drug levels facilitates the brain changes that promote excessive motivation to take the drug (Minogianis et al. 2013; Wakabayashi et al. 2010; Zimmer et al. 2012). Thus, we suggest that drugs, routes of administration and formulations that allow drugs to reach the brain rapidly might increase addiction liability by evoking neuroadaptations in the brain circuits that modulate motivation.

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