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Reversible inactivation of the basolateral amygdala, but not the dorsolateral caudate-putamen, attenuates consolidation of cocaine-cue associative learning in a reinstatement model of drug-seeking

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Abstract

Previous research has shown that the basolateral amygdala (BLA) mediates stimulus-reward learning, including drug-cue associations, while the dorsolateral caudate-putamen (dlCPu) primarily mediates stimulus-response (habit) learning. Recent evidence has indicated that the dlCPu may be critical in cocaine-seeking following extended self-administration, but it remains unknown whether the dlCPu plays a role in early formation of drug-cue associations. The current study used a model of Pavlovian learning to compare the roles of the BLA and dlCPu in the consolidation of cocaine-cue associations that maintain cocaine-seeking during cue-induced reinstatement. Male, Sprague-Dawley rats self-administered cocaine (0.2 mg/50 μ l infusion, IV) in the absence of cues for 6 days (2-h/day). Immediately following a single 1-h classical conditioning (CC) session in which passive cocaine infusions were paired with a light+tone cue, animals received bilateral infusions of the GABA receptor agonists, baclofen+muscimol (B/M, 1.0/0.1 mM), or vehicle into the BLA or dlCPu. Following additional cocaine self-administration (5 days) and subsequent extinction (no cocaine or cues, 7 days), the ability of the previously cocaine-paired cues to reinstate cocaine-seeking was assessed. Inactivation of the BLA, but not the dlCPu, immediately following the CC session impaired the consolidation of cocaine-cue associations as seen by decreased cue-induced reinstatement. These results extend previous findings that the BLA mediates the consolidation of learned associations that drive cocaine-seeking during subsequent reinstatement and indicate that the dlCPu does not play a role during initial stimulus-drug associative learning.

Keywords

rat; relapse; self-administration; stimulus-reward; stimulus-response

Introduction

Relapse to drug use is a significant problem for the treatment of addiction (Dackis & O'Brien, 2001). Cues previously associated with drugs of abuse can trigger craving after long periods of abstinence in human addicts (Childress *et al.*, 1988; Volkow *et al.*, 2006) and animal research demonstrates that previously drug paired cues can robustly reinstate drug-seeking behavior (de Wit & Stewart, 1981; See, 2002). Therefore, investigating the neural substrates that underlie the formation of these associations is imperative to understanding cue-induced relapse.

The basolateral amygdala (BLA) has an established role in the reinstatement of drug-seeking, particularly to drug associated cues (See, 2005). Both excitotoxic lesions (Meil & See, 1997) and pharmacological inactivation (Grimm & See, 2000; Kantak *et al.*, 2002a) of the BLA impair conditioned cued reinstatement. However, BLA lesions do not impair cocaine self-administration (Meil & See, 1997) or cocaine-primed reinstatement (McFarland & Kalivas, 2001), demonstrating the specific involvement of the BLA in attaching incentive value to conditioned reinforcers, and not primary reinforcement itself. These findings are congruent with the recognized role of the BLA in other forms of stimulus-affect learning, such as fear conditioning (LeDoux, 2003) and conditioned place preference (Everitt *et al.*, 1991; Fuchs *et al.*, 2002).

We have previously reported a critical role of the BLA in the acquisition and consolidation of early drug-cue associations using a modified cocaine self-administration model, where cue-cocaine associations are formed during a single classical conditioning (CC) session (Kruzich *et al.*, 2001). Inactivation or pharmacological blockade of the BLA impairs both the acquisition (Kruzich & See, 2001; See *et al.*, 2003; Berglind *et al.*, 2006) and consolidation (Fuchs *et al.*, 2006b; Feltenstein & See, 2007) of cocaine-cue associations, demonstrated by subsequent attenuation of the ability of the conditioned cues to reinstate cocaine-seeking.

Recent research indicates the dorsal striatum, particularly the dorsolateral caudate putamen (dlCPu), is involved in drug-seeking. Human cocaine addicts show increased CPu activity in response to cocaine-associated cues (Garavan *et al.*, 2000; Volkow *et al.*, 2006) and studies in rhesus monkeys have demonstrated increasing involvement of the CPu as cocaine self-administration progresses (Porrino *et al.*, 2004). Finally, dlCPu inactivation impairs contextual reinstatement of cocaine-seeking (Fuchs *et al.*, 2006a; See *et al.*, 2007).

Stimulus-reward learning occurs when a previously neutral stimulus acquires incentive properties when paired with a reward. During the CC session described above, the cues acquire incentive value that later drives reinstatement of cocaine-seeking. In contrast, stimulus-response associations occur when a motor response is reinforced in the presence of a neutral stimulus. The reinforcer strengthens the association between the stimulus and the response, but it is not part of the association (Thorndike, 1933; Hull, 1943). While the BLA plays a significant role in stimulus-reward learning (Cador *et al.*, 1989; Everitt *et al.*, 1991), the dlCPu mediates stimulus-response learning (Mishkin & Petri, 1984; Packard & Knowlton, 2002). The present study examined the respective contribution of these two systems in the consolidation of cocaine-cue associations and subsequent cue-induced reinstatement. Given our previous research demonstrating the involvement of the BLA in this type of learning (See *et al.*, 2003), we predicted that BLA inactivation would impair subsequent cued reinstatement of cocaine-seeking. Little is known about the contribution of the dlCPu to early learning about drug-cue associations. Therefore, the current study utilized a behavioral paradigm well established in our laboratory to investigate this question. However, given the known role of the dlCPu in mediating stimulus-response learning (Packard & Knowlton, 2002), we predicted that dlCPu inactivation would not affect consolidation of early cocaine-cue associations, and their subsequent ability to drive reinstatement of drug-seeking.

Materials and methods

Subjects

Male, Sprague-Dawley rats (Charles-River; 250–275 g) were individually housed on a 12:12 h reverse light-dark cycle, with lights off from 6:00 a.m. to 6:00 p.m. All animals received water *ad libitum*, and were maintained on 25 g of standard rat chow (Harlan, Indianapolis,

IN, USA) per day for the duration of the experiment, unless otherwise noted below. Housing and care of the rats were carried out in accordance with the "Guide for the Care and Use of Laboratory Rats" (Institute of Laboratory Animal Resources on Life Sciences, National Research Council) and all experimental procedures were approved by the MUSC IACUC.

Apparatus

Testing was conducted in standard self-administration chambers (30×20×20 cm, Med-Associates, St Albans, VT, USA) linked to a computerized data collection program (MED PC). Each chamber was equipped with two retractable levers, a white stimulus light, a tone generator (ENV-223HAM, Med Associates), and a house light on the wall opposite the levers. Each chamber was contained within a sound-attenuating cubicle equipped with a ventilation fan.

Surgery

Animals were anesthetized using a mixture of ketamine hydrochloride and xylazine (66 and 1.33 mg/kg, respectively, IP), followed by equithesin (0.5 ml/kg with a solution of 9.72 mg/ml pentobarbital sodium, 42.5 mg/ml chloral hydrate, and 21.3 mg/ml magnesium sulfate heptahydrate dissolved in a 44% propylene glycol, 10% ethanol solution, IP). Ketorolac (2.0 mg/kg, IP) was administered immediately prior to surgery for analgesia. For jugular catheter implantation, an indwelling catheter (Silastic tubing; 0.51 mm i.d. and 0.94 mm o.d.; Dow Corning, Midland, MI, USA) was inserted into the right jugular vein and securely sutured. The other end was led subcutaneously to a back incision, where it was connected to an external silicone harness (Plastics One, Roanoke, VA). Stylets were inserted into the catheters when the rats were not connected to infusion pumps. Immediately following catheter surgery, animals were placed into a stereotaxic frame (Stoelting, Wood Dale, IL, USA) and implanted with bilateral stainless steel guide cannulae (26 gauge; Plastics One, Roanoke, VA) directed towards the dlCPu or the BLA using the appropriate coordinates in mm (dlCPu: AP +1.2, ML ±3.8, DV − 3.4; BLA: AP: −2.7, ML: ±5.0, DV −6.6). Guide cannulae were secured to the skull using steel jeweler's screws and dental acrylic. Following surgery, stylets were placed into the guide cannulae to prevent blockage. For five days following surgery, catheters were flushed daily with 0.1 ml each of 70 U/ml heparinized saline (Elkins-Sinn, Cherry Hill, NJ, USA) and an antibiotic solution cefazolin (10 mg/0.1 ml, Schein Pharmaceuticals, Florham Park, NJ, USA) to maintain catheter patency. During the entire self-administration period, rats received an infusion of 10 U heparinized saline immediately prior to each session, and the cefazolin and 70 U/ml heparinized saline regimen following the session. Catheter patency was assessed occasionally by administration of 2% methohexital sodium (10.0 mg/ml IV; Eli Lilly and Co., Indianapolis, IN, USA), a short-acting barbiturate that produces rapid and reversible muscle flaccidity.

Cocaine self-administration and classical conditioning

Five days following surgery, rats began cocaine self-administration. Infusion tubing for cocaine administration was enclosed in a wire coil and screwed to the external catheter mount on the rat's back. A weighted swivel apparatus (Instech, Plymouth Meeting, PA, USA) allowed for free movement within the chamber. Cocaine hydrochloride (National Institute on Drug Abuse, Research Triangle Park, NC, USA) was mixed in 0.9% sterile saline and filtered (0.45 µm) prior to self-administration, with infusions (0.2 mg/50 µl bolus, IV) delivered by syringe pumps located outside the cubicle. The house light signaled the initiation of the session and remained illuminated throughout the session. Cocaine reinforcement was available along a fixed-ratio 1 (FR-1) schedule for daily 2-h sessions. During each session, a response on the active lever resulted in a 2-s cocaine infusion in the absence of any paired stimulus presentations, followed by a 20-s time-out period. Responding during the time-out or on the inactive lever was recorded, but resulted in no

programmed consequences. Daily self-administration sessions progressed until animals reached a criterion of 6 sessions with at least 10 cocaine infusions per session. Upon reaching criterion, each animal experienced a single 1-h classical conditioning (CC) session with levers unavailable, and passive cocaine infusions were paired with a 5-s light-tone stimulus complex. The number of infusions each animal received during the CC session was equal to the mean number of infusions self-administered by that animal during the first hour of the previous two sessions.

Intracranial infusions

To assess the role of the BLA or the dlCPu in the consolidation of cocaine-cue associations and their subsequent ability to reinstate cocaine-seeking, animals received bilateral intra-BLA or intra-dlCPu infusions of either baclofen/muscimol (B/M, 1.0 and 0.1 mM, respectively) or phosphate buffered saline (PBS) vehicle immediately following the CC session. Injection cannulae (33 gauge; Plastics One) were inserted 2 mm below the tip of the guide cannulae. Bilateral infusions (0.6 μ l/side dlCPu; 0.5 μ l/side - BLA) lasted 2 min, and the cannulae remained for an additional min after the infusion to allow for diffusion. Previous studies have shown that this concentration of B/M and respective bolus amounts impair reinstatement of drug-seeking when infused in the BLA or dlCPu just prior to reinstatement testing (See *et al.*, 2007; Rogers *et al.*, 2008).

Extinction and reinstatement

Following the CC session, animals received an additional 5 days of self-administration sessions on an FR-1 schedule in the absence of conditioned stimulus presentations. After self-administration, rats underwent daily 2-h extinction sessions, during which both the active and inactive lever responses were recorded, but had no programmed consequences. Once extinction criterion was reached (a minimum of 7 sessions with at least 2 consecutive sessions of ≤ 25 active lever responses), animals underwent a conditioned cue reinstatement test, during which each active lever response resulted in a 5-s presentation of the light-tone stimulus in the absence of cocaine reinforcement.

Histology and data analysis

Following testing, animals were anesthetized and transcardially perfused with PBS and 10% formaldehyde solution. Brains were coronally sectioned at a thickness of 75 μ m, and stained with cresyl violet. The sections were examined under light microscopy to determine cannula placement and the most ventral point of each cannula track mapped onto schematics from a rat brain atlas (Paxinos & Watson, 1997). Analyses of active and inactive lever responding and cocaine intake during self-administration, number of CC pairings, and lever responses during extinction and CS-reinstatement testing were conducted using one- or two-way repeated measures ANOVA and one-way ANOVA or t tests, where appropriate. All data were analyzed using SPSS 17.0 (SPSS Inc. Chicago, IL)

Results

Histology

Schematic representations of the most ventral point of bilateral BLA and dlCPu infusion cannulae are indicated in Fig. 1. Infusion cannulae locations (anterior-posterior from bregma) within the BLA ranged from -2.56 to -3.14 , and in the dlCPu from 1.60 to 1.00 . Animals with one or both infusion cannulae tracks located outside of the target regions ($N=3$) were not included in data analyses. The final N /group was: BLA B/M ($N = 9$), BLA Veh ($N = 10$), dlCPu B/M ($N = 8$), and dlCPu Veh ($N = 9$).

BLA

Animals with BLA cannulae readily acquired cocaine self-administration and showed stable responding and cocaine intake by the end of the first 6 days of self-administration (Fig. 2). There were no differences between groups for active and inactive lever responses, or for daily cocaine intake as seen across all days of the self-administration period prior to ($F = 0.002\text{--}1.65$, $P = 0.18\text{--}0.97$) or following ($F = 0.08\text{--}2.87$, $P = 0.12\text{--}0.99$) the CC session. Inactive lever responding across all sessions was routinely very low and did not show any apparent trends. There were no significant differences between groups for the number of cocaine infusions received during the CC session ($F_{1,17} = 0.01$, $P = 0.92$). Additionally, there were no differences between groups for active ($F_{1,17} = 0.06$, $P = 0.81$) or inactive lever ($F_{1,17} = 1.71$, $P = 0.21$) responding across the last two days of extinction sessions (Fig. 2).

Analyses conducted on active lever responding during extinction and the conditioned cued-reinstatement test in animals with BLA cannulae indicated a significant main effect for test ($F_{1,17} = 32.04$, $P = 0.000$), treatment group ($F_{1,17} = 4.492$, $P = 0.049$), and a test $\times$ treatment interaction ($F_{1,17} = 5.37$, $P = 0.033$). Post-hoc analyses revealed that both groups showed significant reinstatement responding above extinction levels (Tukey $P < 0.05$); however, B/M inactivation of the BLA significantly impaired conditioned cued reinstatement responding as compared to PBS vehicle controls (Tukey $P < 0.05$) (Fig. 2). There were no significant differences for inactive lever responding during extinction and the conditioned cued reinstatement test ($F = 0.04\text{--}2.92$, $P = 0.11\text{--}0.84$).

dICPu

Animals with dICPu cannulae readily acquired cocaine self-administration and showed stable responding and cocaine intake by the end of the first 6 days of self-administration (Fig. 3). There were no pre-existing differences between groups for active lever responses or for daily cocaine intake as seen across all days of the self-administration period prior to ($F = 0.08\text{--}1.23$, $P = 0.30\text{--}0.78$), or following ($F = 0.001\text{--}2.09$, $P = 0.17\text{--}0.97$) the CC session. In general, inactive lever responding across all sessions was routinely very low (less than 2/session) and did not show consistent trends. However, a significant difference between groups was seen for inactive lever responses post-CC session ($F_{1,15} = 4.79$, $P = 0.045$), with group means $\pm$ SEM across days as follows (B/M: 1.55 ± 0.46 , Veh: 0.16 ± 0.44). There were no significant differences between groups for the number of cocaine infusions received during the CC session ($F_{1,15} = 2.32$, $P = 0.15$). Additionally, there were no difference between groups for active ($F_{1,15} = 1.16$, $P = 0.30$) or inactive lever ($F_{1,15} = 1.11$, $P = 0.31$) responding across the last two days of extinction training (Fig. 3).

Analyses conducted on active lever responding during extinction and the conditioned cued reinstatement test in animals with dICPu cannulae showed a significant main effect for test ($F_{1,15} = 13.64$, $P = 0.002$), with both groups showing robust reinstatement responding above extinction levels. However, in contrast to animals that received BLA infusions, ANOVA did not reveal a significant main effect for treatment group ($F_{1,15} = 0.01$, $P = 0.91$), or a significant interaction effect ($F_{1,15} = 0.00$, $P = 0.998$). Thus, inactivation of the dICPu failed to impair conditioned cued reinstatement responding as compared to PBS vehicle controls (Fig. 3). For the dICPu, no significant differences were noted for inactive lever responding during extinction and the conditioned cued reinstatement test ($F = 0.18\text{--}3.76$, $P = 0.07\text{--}0.67$).

Discussion

The results of the current study show that BLA, but not dICPu, inactivation with B/M immediately following the CC session impaired consolidation of cocaine-cue associations,

as demonstrated through attenuated cocaine-seeking during subsequent cue induced reinstatement. BLA inactivation following the CC session did not impact subsequent cocaine self-administration, supporting the selective effect of BLA inactivation on conditioned processes. These results extend and support our previous evidence that the BLA plays an important role in the acquisition and consolidation of cocaine-cue associations that drive subsequent cue induced reinstatement of cocaine-seeking (Kruzich & See, 2001; See *et al.*, 2003; Berglind *et al.*, 2006; Fuchs *et al.*, 2006b; Feltenstein & See, 2007). The role of the BLA in drug-paired cue conditioning in this paradigm is consistent with other evidence of BLA-mediated stimulus-reward learning with cocaine (Cador *et al.*, 1989; Everitt *et al.*, 1991; McDonald & White, 1993; Whitelaw *et al.*, 1996), and the fact that BLA lesions do not impair primary reinforcement by cocaine (Whitelaw *et al.*, 1996; Meil & See, 1997). By demonstrating the involvement of the BLA in the consolidation of drug-cue associations that mediate drug-seeking, these results further support the role of the BLA as a key substrate underlying the process by which cues acquire incentive-motivational properties in addiction (for review, see Everitt *et al.*, 1999; Robbins *et al.*, 2008).

The dlCPu has been well established in habitual stimulus-response learning (Mishkin & Petri, 1984; Knowlton *et al.*, 1996; Packard & Knowlton, 2002), and has recently been shown to be involved in craving and relapse (Garavan *et al.*, 2000; Ito *et al.*, 2002; Porrino *et al.*, 2004; Vanderschuren *et al.*, 2005; Fuchs *et al.*, 2006a; Volkow *et al.*, 2006; See *et al.*, 2007). The striatum receives extensive innervation from the cerebral cortex, and the dlCPu in particular receives inputs from the sensory and motor cortical areas (McGeorge & Faull, 1989). These corticostriatal loops may direct the specific motoric outputs in response to stimuli, such as those formed during stimulus-response associations (Wise *et al.*, 1996). Further, dlCPu dependent stimulus-response learning is incremental and acquired over time as reinforcers strengthen the association between stimuli and response (Mishkin & Petri, 1984; Knowlton *et al.*, 1996; Packard & Knowlton, 2002). Recent theories of compulsive drug use propose the formation of maladaptive stimulus-response habits that maintain drug-seeking behavior. While initial drug use is characterized by complex behaviors that are clearly goal directed, these behaviors persist despite negative consequences associated with drug addiction (White, 1996; Everitt & Robbins, 2005; Everitt *et al.*, 2008). This switch to habitual learning may occur through the 'spiraling' loop circuitry in the striatum, in which information progresses in a ventral to dorsal pattern throughout the striatum and associated cortical and midbrain regions (Haber, 2003). Indeed, disconnection between the ventral and dorsolateral striatum through dopamine receptor antagonism in the dorsal striatum contralateral to the unilaterally lesioned nucleus accumbens core impaired cocaine-seeking maintained by a conditioned reinforcer (Belin & Everitt, 2008). In rhesus monkeys trained to self-administer cocaine, chronic cocaine altered striatal glucose utilization in a duration dependent manner, whereby the effects of cocaine were increasingly manifested in the dorsal striatum as the duration of cocaine self-administration progressed (Porrino *et al.*, 2004). Given the connections between the dlCPu and areas such as the BLA (McDonald, 1991) that mediate cued reinstatement (Meil & See, 1997; Grimm & See, 2000; Katak *et al.*, 2002a), it is possible that information about the cues could be encoded by the dorsal striatum and come to later mediate cue driven drug-seeking behavior. However, the lack of effect of dlCPu inactivation on conditioned cued-reinstatement responding is likely due to the fact that the CC session occurred during a single trial and that the animals never actively responded for the cues during self-administration, rather than learning during repeated sessions of operant responding that comprises a typical stimulus-response task mediated by the dlCPu (Mishkin & Petri, 1984; Knowlton *et al.*, 1996; Packard & Knowlton, 2002).

While the dlCPu does not appear to be necessary for consolidation of initial drug-cue associative learning, drug-induced changes in dlCPu function have been implicated in other aspects of addictive behavior. Brain imaging studies with fMRI or PET studies in human

cocaine addicts have demonstrated increased activity (Garavan *et al.*, 2000) and increased dopamine release (Volkow *et al.*, 2006) within the dorsal striatum following presentations of cocaine associated cues. Rats trained on a second order schedule of reinforcement showed increases in extracellular dopamine in the dlCPu in response to cocaine-contingent cue presentation (Ito *et al.*, 2002), while intra-dorsal striatum infusion of dopamine receptor antagonists impaired cocaine-seeking maintained by a conditioned reinforcer (Vanderschuren *et al.*, 2005). While these studies demonstrate that cue motivated responding for cocaine involves the dlCPu following training under a second order schedule of reinforcement, lidocaine inactivation of the dlCPu failed to impair cue induced reinstatement (Kantak *et al.*, 2002b). Similarly, in animals trained to nose poke for cocaine plus a light cue and then trained to maintain a lever response for the light cue alone, B/M inactivation of the dlCPu did not impair cue induced reinstatement of the nose poke response (Di Ciano *et al.*, 2008). Importantly, dlCPu inactivation did impair maintained lever responding for the previously drug-paired reinforcer alone (Di Ciano *et al.*, 2008). These results suggest that the dlCPu may mediate habitual persistent responding for conditioned reinforcers and that conditioned cue-induced reinstatement may involve the retrieval of associations between cues and rewards mediated by the BLA and associated limbic regions (Di Ciano *et al.*, 2008).

While BLA inactivation did not completely block reinstatement responding, response levels were significantly attenuated as compared to the potentiated responding seen in all other groups. The lack of a complete blockade (i.e., down to extinction levels) is consistent with our previous results using sodium channel blockade (Fuchs *et al.*, 2006b) or NMDA receptor antagonism (Feltenstein & See, 2007) at the time of consolidation, and may be due to the limited anatomical extent of the inactivation, particularly along the rostral-caudal extent. Alternatively, inactivation of the BLA at the time of the CC session may not be sufficient to completely block cocaine-cue learning as other pathways (e.g., nucleus accumbens) likely contribute to drug-cue learning (See *et al.*, 2007). Future studies will be directed at other specific areas that may contribute to consolidation of drug-cue learning. Of particular interest is the possible role of the dorsomedial CPu, an area that has been implicated in action-outcome learning (Yin *et al.*, 2005).

A recent study (McDonald & Hong, 2004) examined the dissociating effects of BLA and dlCPu excitotoxic lesions on radial arm maze training to approach a light cue for food reward and a subsequent preference test. BLA-lesioned rats were able to acquire the stimulus-response task normally, but were unable to demonstrate a preference for the lighted arm. Conversely, dlCPu-lesioned rats showed impaired stimulus-response task performance, but showed a preference for the lighted arms. These results suggest that the intact BLA, while unable to maintain the stimulus-response task, still encoded associations between the cue and the reward (McDonald & Hong, 2004). This and similar studies on the roles of the BLA and dlCPu in stimulus-reward and stimulus-response learning, respectively, have demonstrated that these relatively independent systems can be activated simultaneously and in parallel to acquire the appropriate information during any given situation (McDonald & White, 1993).

During prolonged drug use, both amygdalar and dorsal striatal pathways are engaged in the processes that drive drug-taking and drug-seeking behaviors. The current results confirm and extend upon prior studies that demonstrate dissociable roles of the BLA and CPu in appetitive learning, but place this dichotomy within the context of drug-cue learning. While future studies are clearly warranted, our findings support the hypothesis that the dlCPu is less involved in early drug-cue associative processing, but may become more involved in drug-seeking behavior as drug use progresses in an addictive manner (Everitt *et al.*, 2008).

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Abbreviations

BLA	basolateral amygdala
dICPu	dorsolateral caudate putamen
CC	classical conditioning
CS	conditioned stimulus
B/M	baclofen/muscimol

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Figure 1. Schematic diagram of coronal sections (anterior–posterior from bregma) of infusion cannulae placements for the basolateral amygdala (left) and the dorsolateral caudate putamen (right) (adapted from Paxinos & Watson, 1997).

Figure 2.

Mean ($\pm$ SEM) active (top) and inactive (bottom) lever responses for the last two days of self-administration (SA) phases I and II, extinction (EXT), and during the CS-reinstatement test. Animals received bilateral intra-BLA infusions of vehicle or B/M immediately following the CC session. Significant differences are indicated as compared to extinction levels (* $P < 0.05$) or vehicle ($\dagger P < 0.05$).

Figure 3.

Mean ($\pm$ SEM) active (top) and inactive (bottom) lever responses for the last two days of self-administration (SA) phases I and II, extinction (EXT), and during the CS-reinstatement test. Animals received bilateral intra-CPu infusions of vehicle or B/M immediately following the CC session. Significant differences are indicated as compared to extinction levels (* $P < 0.01$).