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THE SEROTONIN (5-HT) 5-HT$_{2A}$ RECEPTOR: ASSOCIATION WITH INHERENT AND COCAINE-EVOKED BEHAVIORAL DISINHIBITION IN RATS

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Abstract

Alterations in the balance of functional activity within the serotonin (5-HT) system are hypothesized to underlie impulse control. Cocaine-dependent subjects consistently demonstrate greater impulsivity relative to non-drug using control subjects. Preclinical studies suggest that the 5-HT$_{2A}$ receptor (5-HT$_{2A}$R) contributes to the regulation of impulsive behavior and also mediates some of the behavioral effects of cocaine. We hypothesized that the selective 5-HT$_{2A}$R antagonist M100907 would reduce inherent levels of impulsivity and attenuate impulsive responding induced by cocaine in two animal models of impulsivity, the differential reinforcement of low rate (DRL) task and the one-choice serial reaction time (1-CSRT) task. M100907 reduced rates of responding in the DRL task and premature responding in the 1-CSRT task. Conversely, cocaine disrupted rates of responding in the DRL task and increased premature responding in the 1-CSRT task. M100907 attenuated cocaine-induced increases in specific markers of behavioral disinhibition in the DRL and 1-CSRT tasks. These results suggest that the 5-HT$_{2A}$R regulates inherent impulsivity, and that blockade of the 5-HT$_{2A}$R alleviates specific aspects of elevated levels of impulsivity induced by cocaine exposure. These data point to the 5-HT$_{2A}$R as an important regulatory substrate in impulse control.

Keywords

cocaine; impulsivity; 5-HT$_{2A}$ receptor; behavioral disinhibition; differential reinforcement of low rate task; one-choice serial reaction time task; rat

INTRODUCTION

Impulsivity is a multidimensional personality trait characterized by poor inhibitory control over behavior in response to internal or external stimuli, the failure to consider the

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consequences of these reactions, and a preference for immediate rather than delayed reinforcement (Evenden 1999; Moeller *et al.* 2001a). Impulsive choice (or impulsive decision-making) and impulsive action (or behavioral disinhibition, *i.e.*, the diminished ability to withhold inappropriate behavioral responses) are two primary dimensions of impulsivity that have been associated with addictive behaviors (*e.g.*, binge eating, gambling, and drug abuse). Various aspects of drug abuse, including initial drug-taking, the transition from casual to compulsive drug use, the maintenance of drug-seeking behaviors as well as the penchant to reinstate drug-seeking behaviors in both humans (Moeller *et al.* 2001a, 2002, 2004; Coffey *et al.* 2003) and laboratory animals (Perry *et al.* 2005; Belin *et al.* 2008; Dalley *et al.* 2007; Diergaarde *et al.* 2008) appear to be correlated with the individual degree of impulsivity (Jentsch & Taylor 1999; de Wit & Richards 2004; Moeller *et al.* 2001b; Tarter *et al.* 2007; Belin *et al.* 2008). The behavioral and neurochemical underpinnings of impulsivity in relation to cocaine intoxication and dependence have received only limited attention to date.

Impulse control is linked with alterations in functional activity of the monoamine [serotonin (5-hydroxytryptamine, 5-HT), dopamine (DA), norepinephrine (NE)] systems (for review, see Pattij & Vanderschuren 2008). Specifically, alterations in synaptic levels of either 5-HT, DA, or NE can disrupt the balance of the 5-HT:DA:NE interaction and may represent a neurobiological mechanism underlying impulsivity (Winstanley *et al.* 2003; Winstanley *et al.* 2006b). There is extensive evidence that serotonergic lesions, selective 5-HT reuptake inhibitors and other non-selective pharmacological manipulations of the 5-HT system alter performance in animal models of impulsivity (Winstanley *et al.* 2004a, b; Harrison *et al.* 1997; Koskinen *et al.* 2000; Koskinen & Sirvio 2001; Marek *et al.* 1989). In the past, studies on the role of 5-HT in animal models of impulsivity relied on nonselective pharmacological manipulation of the serotonergic system yielding mixed and sometimes complicated results, most likely due to the actions of 5-HT at multiple receptors (Winstanley *et al.* 2003, 2004a,b, 2006a; Harrison *et al.* 1997; Fletcher *et al.* 2007, 2009; Higgins *et al.* 2003; Robinson *et al.* 2008; Liao & Chang 2001) as well as within multiple neurotransmitter circuits, including DA and NE (Higgins *et al.* 2003; Winstanley *et al.* 2005; Bubar & Cunningham 2008). However, the development of compounds that act selectively at specific 5-HT receptors has enabled more defined analyses of 5-HT receptor involvement in impulsive behavior. Recent studies with antagonists selective for the 5-HT_{2A}R (*e.g.*, M100907) revealed that blockade of the 5-HT_{2A}R decreased impulsive behaviors in animal models of impulsive action (Winstanley *et al.* 2003, 2004b; Marek *et al.* 2005; Higgins *et al.* 2003; Robinson *et al.* 2008), suggesting that tonic activation of the 5-HT_{2A}R attunes the 5-HT:DA:NE balance (Bubar & Cunningham 2008) that regulates inherent impulsivity.

The psychoactive and behavioral effects of cocaine result from blockade of monoamine reuptake, enhancing the concentrations of 5-HT, DA, and NE in the synapse (Koe 1976) and subsequent activation of monoamine receptors within the limbic-corticostriatal pathway (Koob 1992). Neurotransmission through 5-HT_{2A}R also regulates many of the behavioral and neurochemical effects of cocaine (Bubar & Cunningham 2008), including its locomotor stimulant (Fletcher *et al.* 2002; McMahon & Cunningham 2001), discriminative stimulus properties (McMahon & Cunningham 2001; Filip *et al.* 2006) as well as the incentive-motivational value of cocaine-associated cues (Nic Dhonnchadha *et al.* 2009; Burmeister *et al.* 2004; Filip 2005). Thus, the 5-HT_{2A}R may be an important mediator in the neurobiological relationship between impulsivity and cocaine addiction.

Despite the development of multiple animal models of impulsivity, few attempts have been made to use more than one animal model within a single study to identify which dimensions of impulsive action are altered following pharmacological manipulations (Winstanley *et al.* 2004b; Fletcher *et al.* 2009). The purpose of this study was to employ two models of

behavioral disinhibition [the differential reinforcement of low-rate (DRL) task and the 1-choice serial reaction time (1-CSRT) task] to measure the effect of 5-HT_{2A}R antagonism on inherent and cocaine-evoked behavioral disinhibition.

The DRL task is an operant task which requires the rat to withhold a behavioral response until a certain time interval has elapsed in order to obtain a reinforcer. Responses made prior to the completion of the schedule are not reinforced, and the schedule clock is reset. Animals that exhibit high levels of impulsive-like behaviors tend to have higher rates of premature responding and, as a result, obtain fewer reinforcers (Stoffel & Cunningham 2008). This task was selected for various reasons. The DRL task has high face validity: an analogous model has been successfully utilized in humans to distinguish between impulsive and non-impulsive subjects (van den Broek *et al.* 1987). Second, DRL schedules in rodents have demonstrated robust sensitivity to the effects of psychostimulants (Sabol *et al.* 1995; Wang *et al.* 2001; Wenger & Wright 1990; Stoffel & Cunningham 2008) and serotonergic manipulations (Ardayfio *et al.* 2008; Jolly *et al.* 1999; Sokolowski & Seiden 1999; O'Donnell *et al.* 2005).

The 1-CSRT task is an operant task in which reinforcement is obtained for detecting and correctly responding to brief presentations of a visual target presented regularly in a spatially predictable location (Dalley *et al.* 2002). In the 1-CSRT task, a single stimulus light and nose poke hole is utilized; the rat needs only to predict when the stimulus will occur, then emit a nosepoke in the active (lit) aperture to earn a reinforcer. Thus, the 1-CSRT task provides a model of behavioral disinhibition independent from complex visuospatial attentional processes. The measure of anticipatory (premature) responding before presentation of the visual target provides the ability to study behavioral disinhibition. A variant of the 1-CSRT task is the 5-CSRT task that requires more demand on visuospatial attentional processes than the 1-CSRT task; the CSRT task in animals (Robbins 2002) is analogous to the continuous performance task in humans (Beck *et al.* 1956; Mirsky & Rosvold 1960; Robbins 2002), lending face validity to the use of CSRT tasks in preclinical studies of impulsivity. Premature responding in CSRT tasks is enhanced by the psychostimulant amphetamine (Cole & Robbins 1989; Loos *et al.* 2010) and is also highly sensitive to manipulations of serotonergic neurotransmission, *e.g.*, blockade of 5-HT_{2A}R (for reviews, see Pattij & Vanderschuren 2008; Robbins 2002). Furthermore, global serotonergic depletion within the rat forebrain enhances premature responding (*i.e.*, behavioral disinhibition) in CSRT tasks (Winstanley *et al.* 2004a; Harrison *et al.* 1997; Fletcher *et al.* 2009).

The use of two or more distinct behavioral disinhibition assays allows better validation of the neurochemical systems involved in individual aspects of impulsivity. Thus, we tested the hypotheses that the 5-HT_{2A}R represents a neurobiological substrate of impulsive action and acts as a functional rheostat to maintain the balance of inherent levels of impulsivity as well as cocaine-disrupted impulsive action. Specifically, we hypothesized that the 5-HT_{2A}R antagonist M100907 would reduce inherent behavioral disinhibition as well as attenuate cocaine-evoked behavioral disinhibition as measured with both the DRL and 1-CSRT tasks.

METHODS

Subjects

Male Sprague-Dawley rats (Harlan Sprague-Dawley, Inc., Indianapolis, IN) weighing 250–275 g at the time of arrival were used (N=24). Rats were allowed to acclimate for 5–6 days to a colony room at a constant temperature (21–23°C) and humidity (40–50%) on a 12 hr light-dark cycle (lights on at 07:00 hr). Rats were housed two per cage during operant training. For DRL task training, food was freely available for the duration of all

experiments; however, water intake was restricted to that available during operant training sessions, after sessions (10–15 min) and on weekends (approx 36 hrs). For 1-CSRT task training, rats were food restricted to 90% free-feeding weight for the duration of all experiments; water was freely available except during daily 30–60 min operant sessions. All experiments were carried out in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* (Council, 1996) and with the approval of the UTMB Institutional Animal Care and Use Committee.

5-HT_{2A}R regulation of inherent behavioral disinhibition and cocaine-evoked disruption of behavioral disinhibition in the DRL-20 sec task

Apparatus—DRL task procedures were carried out in eight two-lever operant chambers housed in sound-attenuating chambers (Lafayette Instruments, Lafayette, IN, or Med Associates, St. Albans, VT). The chambers contained two levers with a water dispenser centered between the two levers. Illumination was provided by a 28-V houselight. Ventilation and sound masking were provided by a fan mounted in the wall of the sound-attenuating cabinet. An interface (Med Associates) connected the chambers to a PC computer running Med PC for Windows software (Med Associates) that controlled and recorded all experimental events.

Training—After acclimation to the colony room, rats (n=8–16/group) were handled and weighed daily for 3–5 days after which DRL task training began. Procedures for the DRL task were performed as previously described with minor modifications (Stoffel & Cunningham 2008). All DRL task training and testing sessions were 60 min in length and were conducted between 10:00 and 15:00 hr on weekdays (Monday-Friday). Rats were placed into DRL task operant chambers following 23 hrs of water restriction. For all rats, the left lever was designated as the “active” lever and the right lever was the “inactive” lever. Rats were initially trained on a DRL 5-s schedule of reinforcement task. Each session began with illumination of the house light. Responses on the active lever that were at least 5 s apart resulted in the delivery of a reinforcer (water), and the house light was extinguished for a brief (2 sec) inter-trial interval (ITI). Responses on the active lever that were not at least 5 s apart initiated the ITI, and reset the interval timer to zero, resulting in an additional 5 s delay to the next available reinforcer. Responses on the inactive lever were recorded, but had no scheduled consequences. Once rats had obtained at least 100 reinforcers for two consecutive days, the DRL task interval requirement for the next session was increased to 20 s. Rats remained on the DRL 20-sschedule until stable responding was achieved; responding was considered stable when the standard error of the mean for the total response rate was less than 10% of the mean response rate for five consecutive sessions (Li *et al.* 1989).

After responding was stabilized, pretreatment with M100907 (0.01, 0.03, 0.1, 0.3, 0.5 mg/kg, i.p.; synthesized by Kenner Rice, National Institute on Drug Abuse, Bethesda, MD) or vehicle (1% Tween 80 in saline, i.p.) occurred 15 min prior to an injection with saline (1 ml/kg, i.p.) or cocaine (10 mg/kg, i.p.; National Institute on Drug Abuse, Research Triangle, NC) immediately before the start of the DRL task session. Rats received saline or vehicle injections on Wednesdays and M100907 or cocaine injections on Thursdays; the order of M100907 and cocaine injections was randomized across all rats in a within-subjects design.

Data Analysis—During the DRL-20 s task sessions, the total number of responses per session (on both active and inactive levers), and total number of reinforcers obtained per session were recorded for each 60 min session. Once rats were well-trained, inactive lever responses consistently accounted for less than 5% of total responses during DRL-20 s task sessions. The response rate was calculated as total number of responses per min during the 60-min DRL-20 s task sessions. The total number of reinforcers obtained was used as a

general indication of behavioral disinhibition in each rat; rats with high behavioral disinhibition (*i.e.*, poor inhibitory control) earn fewer reinforcers (Stoffel & Cunningham 2008). Response rate and reinforcers obtained on test sessions (M100907 ± cocaine or saline) are presented as the percentage of values observed on the maintenance session immediately prior to the test session; prior to this maintenance session, rats are injected with vehicle+saline (control). Inter-response times (IRT) were calculated for DRL-20 s responding on the last session of stable baseline responding and on the session during which saline, cocaine or M100907 was administered; IRT frequencies were tabulated and converted to relative frequencies by dividing the frequency of each IRT value by the total number of responses made during the session. Relative frequencies were plotted as histograms (in 2-s bins), and the mean, median and mode were calculated for each IRT distribution. The frequency of burst responses represents an additional facet of behavioral disinhibition and was calculated based on the relative frequencies of responses made during the burst component of the IRT distribution (< 4 sec) (Jolly *et al.* 1999; Fletcher 1995; Pattij *et al.* 2003, 2004; Wogar *et al.* 1992). Modified peak shift analysis was performed by comparing the shift in the peak relative frequency for each drug treatment versus the control peak relative frequency (Richards *et al.* 1993).

The effects of administration of M100907 (pretreatment) in the presence or absence of cocaine administration (treatment) on DRL-20 s task response measures [response rate, number of reinforcers obtained, IRT mean, median, mode values, burst responding, peak shifts] were analyzed with a two-way repeated measures ANOVA [pretreatment, treatment] using the general linear model (GLM) procedure (Keppel 1973). *A priori* comparisons to analyze the effects of M100907 on inherent behavioral disinhibition or the effects of M100907 on cocaine-evoked behavioral disinhibition were defined before the start of experiment; therefore, one-way repeated measures ANOVA and preplanned comparisons of the treatment means versus control were made with Dunnett's procedure. All statistical analyses were conducted with SAS for Windows version 8.2. The alpha level for all analyses was set at $p<0.05$. Graphic presentations of data are provided separately for the effects of M100907 in the absence (Fig. 1) and presence of cocaine (Fig. 2) to allow clear descriptions of effects on inherent and cocaine-evoked behavioral disinhibition, respectively.

5-HT_{2A}R regulation of inherent behavioral disinhibition and cocaine-evoked disruption of behavioral disinhibition in the 1-CSRT task

Apparatus—1-CSRT task procedures took place in eight standard five-hole nosepoke operant chambers (Med Associates, Roanoke, VA) contained within a ventilated and sound-attenuating chamber. Each chamber was fitted with an array of five evenly-spaced response apertures (2.5 × 2.5 × 2.2 cm) positioned 2 cm above a bar floor, and each aperture contained a stimulus light. Nosepoke responses into these apertures were detected by a horizontally-positioned infrared beam located 1 cm from the entrance to each hole. The chambers are also fitted on the opposite wall with a houselight, food tray, and an external pellet dispenser capable of delivering 45 mg pellets (Dustless Precision pelletsR, Bio-Serv, Frenchtown, NJ) to the food tray. The chambers were connected via an interface (Med Associates) to a PC computer running Med PC for Windows software (Med Associates) that controlled and recorded all experimental events.

Training—Rats (n=8) were allowed one week to acclimate to the colony after which food restriction began. Rats were weighed daily to ensure that body weights were maintained at 90% of free-feeding levels during an initial seven days of food restriction prior to initiation of 1-CSRT task training. Training began with a pre-training stage (PT-1) in which the rat was habituated to the test chamber and introduced to nosepoke responding for food pellets. During PT-1, all responses made in the correctly lit (center) hole resulted in the illumination

of the magazine light and presentation of a single food pellet. Retrieval of the food pellet from the food magazine resulted in termination of the magazine light, and after a 2-s intertrial interval (ITI) the next trial began with the stimulus (center) hole illumination. After reaching a criteria of 30 correct trials (*i.e.*, reinforced trials) within the 60-min daily session, rats advanced to pre-training stage 2 (PT-2) which required a correct response in a given timeframe to receive a reinforcer. During PT-2, the stimulus light was illuminated for 60 s (stimulus duration); subsequently, the stimulus light was extinguished for 60 s (limited hold). Any correct response made during either time period (*i.e.*, stimulus duration or limited hold) resulted in presentation of the reinforcer; incorrect responses (nosepoke in any hole other than the center hole) and/or omitted responses were recorded and now resulted in a 5-s time out period in which the house light was illuminated and no reinforcer delivered. In PT-2, premature responses were recorded but did not result in a time out period. The training stages thereafter were each comprised of daily sessions of 100 trials to be completed in a maximum of 30 min; each training stage involved incrementally lowering the stimulus duration with a 5-s limited hold and an ITI of 5 s. Thus, a maximum of 100 correct responses in a session would result in a maximum of 100 reinforcers delivered; incorrect or premature responses or omissions resulted in a 5-s time out period and a reduction in potential reinforcers obtained. Rats were required to meet an acquisition criteria of a minimum of 50 correct responses, >80% accuracy [correct responses/(correct + incorrect) × 100] and <20% omissions (omitted responses/trials completed × 100) to move from one training stage to the next.

Pharmacological test sessions commenced after animals met the acquisition criteria of >80% accuracy and <20% omissions for at least five consecutive training stages on the final training stage (0.5 s stimulus duration, 5 s limited hold, 5 s ITI) with less than 15% variability across training days. Pretreatment with M100907 (0.01, 0.03, 0.1, 0.3, 0.5 mg/kg, i.p) or vehicle (1% Tween 80 in saline, i.p.) occurred 15 min prior to an injection with saline (1 ml/kg, i.p.) or cocaine (10 mg/kg, i.p) immediately before the start of the 1-CSRT task session. Rats received saline or vehicle injections on Mondays and Thursdays and M100907 or cocaine injections on Tuesdays and Fridays; the order of M100907 and cocaine injections was randomized across all rats in a within-subjects design.

Data Analysis—During the 1-CSRT task, the total number of responses (correct, incorrect, omissions, and premature) as well as the latency to start the task (sec) and time to finish (min) were recorded. As rats were well-trained upon achieving the task criterion, incorrect responses consistently accounted for less than 5% of total responses during 1-CSRT task test sessions. Percent accuracy [(correct responses/correct + incorrect) × 100] was used as a general indication of the attentional capacity of each rat. Percent omissions (omitted responses/trials completed × 100) during the 1-CSRT task were indicative of the motivation level of each rat to perform the task. Responses during the ITI (premature responses) and total number of reinforcers obtained (correct responses) during the 1-CSRT task session were used to assess behavioral disinhibition. Premature responses and total number of reinforcers obtained on test sessions (M100907 ± cocaine or saline) are presented as the percentage of values observed on the maintenance session immediately prior to the test session; prior to this maintenance session, rats are injected with vehicle+saline (control).

Statistical analyses (two-way repeated measures ANOVA) of the effects of M100907 (pretreatment) alone or in presence of cocaine (treatment) administration on 1-CSRT task measures [% accuracy, % omissions, premature responses, reinforcers obtained, latency to start, time to finish] were conducted as described above for the DRL-20 sec task data analysis. Graphic presentations of data are provided separately for the effects of M100907 in the absence (Fig. 3) and presence of cocaine (Fig. 4) to allow clear descriptions of effects on inherent and cocaine-evoked behavioral disinhibition, respectively.

RESULTS

5-HT$_{2A}$R regulation of inherent behavioral disinhibition and cocaine-evoked disruption of behavioral disinhibition in the DRL-20 sec task

We evaluated rats injected with M100907 or vehicle (pretreatment) prior to saline or cocaine injection (treatment) in the DRL-20 s task to determine the effects of M100907 on inherent or cocaine-evoked behavioral disinhibition; the response rate, number of reinforcers obtained, IRT distribution, burst responding, and peak shift were the measures analyzed. Significant main effects of pretreatment ($F_{5,58} = 2.46$, $p<0.05$), treatment ($F_{1,58} = 73.73$, $p<0.001$) and pretreatment × treatment interaction ($F_{5,58} = 3.85$, $p<0.01$) on the *response rate* in the DRL-20 sec task were observed. There were significant main effects of pretreatment ($F_{5,58} = 2.76$, $p<0.05$) and treatment ($F_{1,58} = 108.43$, $p<0.001$), but no significant pretreatment × treatment interaction ($F_{5,58} = 1.51$, n.s.), on the *number of reinforcers obtained* in the DRL-20 s task. A significant main effect of treatment ($F_{1,58} = 105.74$, $p<0.001$) on the *mean of the IRT distribution* was observed, but the effect of pretreatment ($F_{5,58} = 1.68$, n.s.) and the pretreatment × treatment interaction ($F_{5,58} = 1.56$, n.s.) were nonsignificant. There was a trend toward a main effect of pretreatment ($F_{5,58} = 2.18$, $p=0.06$), a significant main effect of treatment ($F_{1,58} = 137.22$, $p<0.001$), but no significant pretreatment × treatment interaction ($F_{5,58} = 1.31$, n.s.) for *the median of the IRT distribution*. There was a significant main effect of treatment ($F_{1,58} = 78.39$, $p<0.001$), but no significant effect of pretreatment ($F_{5,58} = 0.82$, n.s.) or pretreatment × treatment interaction ($F_{5,58} = 2.08$, n.s.), for the *mode of the IRT distribution*. There was a significant main effect of treatment ($F_{1,58} = 11.40$, $p<0.01$), no significant main effect of pretreatment ($F_{5,58} = 1.85$, n.s), and a trend toward a pretreatment × treatment interaction ($F_{5,58} = 2.23$, $p=0.06$), on *burst responding*. There were significant main effects of treatment ($F_{1,58} = 79.21$, $p<0.001$) and of pretreatment ($F_{5,58} = 5.03$, $p<0.001$), and a trend toward a pretreatment × treatment interaction ($F_{5,58} = 2.14$, $p=0.07$), on the *peak shift in the IRT distribution*.

Effects of M100907 on inherent behavioral disinhibition in the DRL-20 sec task

—We analyzed the data for rats pretreated with M100907 or vehicle prior to saline treatment in the DRL-20 s task to determine the effects of M100907 on inherent behavioral disinhibition. Figure 1 displays the response rate (Fig. 1A) and the number of reinforcers obtained (Fig. 1B) for vehicle and each dose of M100907; data are presented as a percentage of the response rate and number of reinforcers obtained on the vehicle+saline administration session (control) that preceded each dose evaluated. The average response rate/session across all control sessions (see Methods) was 3.13 ± 0.1 responses/min, while the number of reinforcers obtained/session was 50.51 ± 3.1. M100907 administration altered behavioral disinhibition in the DRL-20 sec task (Fig. 1). A significant main effect of pretreatment on response rate ($F_{5,50} = 3.45$, $p<0.01$) was observed; planned comparisons with Dunnett's procedure showed that the doses of 0.1, 0.3 and 0.5 mg/kg M100907 decreased the response rate versus control (Fig. 1A). A significant main effect of pretreatment was also observed for number of reinforcers obtained ($F_{5,58} = 5.55$, $p<0.001$); planned comparisons with Dunnett's procedure showed that the doses of 0.01, 0.03, 0.1, and 0.3 mg/kg M100907 increased the number of reinforcers obtained versus control (Fig. 1B).

The descriptive statistics for IRT distribution for each dose of M100907 administered are presented in Table 1. A significant main effect of pretreatment on the mean ($F_{5,58} = 2.51$, $p<0.05$) and median ($F_{5,58} = 3.53$, $p<0.01$), but not the mode ($F_{5,58} = 1.69$, n.s), of the IRT distribution were observed. Planned comparisons with Dunnett's procedure showed that 0.1 mg/kg of M100907 increased the mean of the IRT distribution versus control; 0.1 and 0.5 mg/kg M100907 increased the median of the IRT distribution versus control; 0.1 mg/kg

M100907 increased the mode of the IRT distribution versus control (Table 1). The IRT distributions for control and 0.1 mg/kg M100907 are shown across 2-s time bins (Fig. 1C). There was no significant main effect of pretreatment ($F_{5,58} = 1.36$, n.s.) on burst responding versus control. There was a significant main effect of pretreatment ($F_{6,73} = 13.21$, $p<0.001$) on the peak shift in the IRT distribution; planned comparisons with Dunnett's procedure showed that M100907 at 0.1 (Fig. 1C) and 0.5 mg/kg (data not shown) shifted the IRT distribution right versus control.

Effects of M100907 on cocaine-evoked disruption of behavioral disinhibition in the DRL-20 sec task—We analyzed the data for rats pretreated with M100907 or vehicle prior to cocaine treatment in the DRL-20 s task to determine the effects of M100907 on cocaine-evoked behavioral disinhibition. Figure 2 displays the response rate (Fig. 2A) and the number of reinforcers obtained (Fig. 2B) for vehicle and each dose of M100907 (pretreatment) in the presence of cocaine (treatment); data are presented as a percentage of the response rate and number of reinforcers obtained on the vehicle+saline administration session (control) that preceded each dose evaluated. The average response rate/session across all control sessions (see Methods) in vehicle+saline-treated animals was 3.13 ± 0.1 responses/min, while the number of reinforcers obtained/session was 50.51 ± 3.1. Cocaine administration altered behavioral disinhibition in the DRL-20 sec task (Fig. 2). A significant main effect of treatment on response rate ($F_{6,72} = 5.66$, $p<0.001$) was observed. Planned comparisons with Dunnett's procedure showed that cocaine increased the response rate versus control (Fig. 2A, $p<0.05$); 0.01 and 0.3 mg/kg M100907 attenuated the cocaine-induced increases in response rate (Fig. 2A; $p<0.05$). Consistent with these changes in response rate, we also observed changes in the number of reinforcers obtained following pharmacological manipulations in the DRL-20 s task. A significant main effect of treatment on reinforcers obtained ($F_{6,69} = 5.19$, $p<0.001$) was observed. Planned comparisons with Dunnett's procedure showed that cocaine decreased the number of reinforcers obtained versus control (Fig. 2B; $p<0.05$); and 0.3 mg/kg M100907 prevented the cocaine-induced decrease in number of reinforcers obtained (Fig. 2B; $p<0.05$).

The descriptive statistics for IRT distribution for each dose of M100907 in the presence of cocaine are presented in Table 2. Significant main effects of treatment on the mean ($F_{6,73} = 2.73$, $p<0.05$), median ($F_{6,73} = 3.35$, $p<0.01$), and the mode ($F_{6,73} = 3.5$, $p<0.01$), of the IRT distribution were observed. Planned comparisons with Dunnett's procedure showed that cocaine decreased the mean ($p<0.05$), median ($p<0.05$), and mode ($p<0.05$) of the IRT distribution versus control (Table 2); M100907 did not significantly alter the cocaine-evoked IRT mean (n.s.), median (n.s.), or mode (n.s.) (Table 2). The IRT distributions for cocaine and a representative dose of M100907 (0.3 mg/kg) + cocaine (Fig. 2C) are shown across 2-s time bins. A significant main effect of treatment on burst responding ($F_{6,69} = 2.60$, $p<0.05$) was observed. Planned comparisons with Dunnett's procedure showed that cocaine enhanced burst responding versus control ($p<0.05$); and M100907 at 0.01, 0.3 and 0.5 mg/kg attenuated the cocaine-induced increase in burst responding ($p<0.05$). A significant main effect of treatment on the peak shift in the IRT distribution ($F_{6,71} = 5.04$, $p<0.001$) was observed. Planned comparisons with Dunnett's procedure showed that cocaine shifted the peak IRT distribution to the left versus control (Fig. 2C, $p<0.05$); and M100907 at 0.3 mg/kg shifted the cocaine-evoked peak IRT distribution right to control levels (Fig. 2C, $p<0.05$).

5-HT_{2A}R regulation of inherent behavioral disinhibition and cocaine-evoked disruption of behavioral disinhibition in the 1-CSRT Task

We analyzed the data for rats pretreated with M100907 or vehicle prior to saline or cocaine treatment in the 1-CSRT task to determine the effects of M100907 on inherent or cocaine-evoked behavioral disinhibition. Significant main effect of pretreatment ($F_{5,42} = 4.57$,

$p<0.01$) and treatment ($F_{1,42} = 46.58$, $p<0.001$), but no significant pretreatment × treatment interaction ($F_{5,42} = 1.10$, n.s.), on *premature responses* in the 1-CSRT task were observed. Significant main effects of pretreatment ($F_{5,42} = 2.53$, $p<0.05$) and treatment ($F_{1,42} = 93.88$, $p<0.001$), but no significant pretreatment × treatment interaction ($F_{5,42} = 0.55$, n.s.), on *reinforcers obtained* in the 1-CSRT task were observed. The *% accuracy* measure in the 1-CSRT task exhibited no significant main effect of pretreatment ($F_{5,42} = 1.16$, n.s.), a significant main effect of treatment ($F_{1,42} = 7.73$, $p<0.01$) and no significant pretreatment × treatment interaction ($F_{5,42} = 0.41$, n.s.). The *% omissions* made in the 1-CSRT task exhibited no significant main effect of pretreatment ($F_{5,42} = 0.63$, n.s.), a significant main effect of treatment ($F_{1,42} = 5.84$, $p<0.05$) and no significant pretreatment × treatment interaction ($F_{5,42} = 0.74$, n.s.). Analysis of the *latency to start* the 1-CSRT task showed no significant main effect of pretreatment ($F_{5,40} = 0.45$, n.s.) or treatment ($F_{1,40} = 0.04$, n.s.) or pretreatment × treatment interaction ($F_{5,40} = 0.9$, n.s.). Analysis of *time to finish* the 1-CSRT task showed no significant effect of pretreatment ($F_{5,42} = 0.5$, n.s.), a significant main effect of treatment ($F_{1,42} = 12.59$, $p<0.05$) and no significant pretreatment × treatment interaction ($F_{5,42} = 0.21$, n.s.).

Effects of M100907 on inherent behavioral disinhibition in the 1-CSRT task— The effects of M100907 on behavioral disinhibition indices in the 1-CSRT task were evaluated in rats pretreated with M100907 or vehicle prior to saline treatment in the 1-CSRT task. Figure 3 displays the number of premature responses (Fig. 3A) and reinforcers obtained (Fig. 3B) for vehicle and each dose of M100907 tested; data are presented as a percentage of the number of responses made or reinforcers obtained on the vehicle+saline administration session (control) that preceded each dose evaluated. The average number of premature responses/session across all control sessions (see Methods) in vehicle+saline-treated animals was 31.47 ± 1.8, while the number of reinforcers obtained/session was 61.94 ± 2.1. M100907 administration significantly altered behavioral disinhibition in the 1-CSRT task (Fig. 3). There was a significant main effect of M100907 on premature responses ($F_{5,42} = 10.07$, $p<0.001$); planned comparisons with Dunnett's procedure showed 0.03, 0.1, 0.3 and 0.5 mg/kg M100907 decreased premature responses versus control (Fig. 3A). There was a significant main effect of M100907 on the number of reinforcers obtained ($F_{5,42} = 2.72$, $p<0.05$); planned comparisons with Dunnett's procedure showed 0.03, 0.1, and 0.3 mg/kg M100907 increased the number of reinforcers obtained responses versus control (Fig. 3B).

Descriptive statistics for % accuracy, % omissions, latency to start and time to finish the 1-CSRT task for vehicle, cocaine and each dose of M100907 administered are presented in Table 3. There were no significant main effects of pretreatment on % accuracy ($F_{5,42} = 0.63$, n.s.), % omissions ($F_{5,36} = 0.64$, n.s.), latency to start ($F_{5,40} = 0.72$, n.s.) or time to finish ($F_{5,42} = 1.05$, n.s.) in the 1-CSRT task (Table 3).

Effects of M100907 on cocaine-evoked disruption of behavioral disinhibition in the 1-CSRT task—Figure 4 displays the number of premature responses (Fig. 4A) and reinforcers obtained (Fig. 4B) for each dose of M100907 in the presence of cocaine; data are presented as a percentage of the number of responses made or number of reinforcers obtained on the vehicle+saline administration session (control) that preceded each dose evaluated. The average number of premature responses/session across all control sessions (see Methods) in vehicle+saline-treated animals was 31.47 ± 1.8, while the number of reinforcers obtained/session was 61.94 ± 2.1. Cocaine administration altered behavioral disinhibition in the 1-CSRT task (Fig. 4). A significant main effect of treatment on premature responses ($F_{6,48} = 2.36$, $p<0.05$) was observed. Planned comparisons with Dunnett's procedure showed that cocaine increased the number of premature responses versus control (Fig. 4A; $p<0.05$); and 0.5 mg/kg M100907 prevented the cocaine-induced increase in premature responses (Fig. 4A; $p<0.05$). There was a significant main effect of

treatment on the number of reinforcers obtained ($F_{6,49} = 2.75$, $p<0.05$). Planned comparisons with Dunnett's procedure showed that cocaine increased the number of premature responses versus control (Fig. 4B; $p<0.05$); M100907 did not alter the number of reinforcers obtained after 10 mg/kg cocaine treatment (Fig. 4B; n.s.).

Descriptive statistics for % accuracy, % omissions, latency to start and time to finish the 1-CSRT task for vehicle, cocaine and each dose of M100907 in combination with cocaine are presented in Table 4. There were no significant main effects of treatment on % accuracy ($F_{6,49} = 1.01$, n.s.), % omissions ($F_{6,41} = 0.88$, n.s.), latency to start ($F_{6,48} = 0.55$, n.s.) or time to finish ($F_{6,49} = 0.74$, n.s.) in the 1-CSRT task (Table 4). Cocaine did not alter % accuracy, % omissions, the latency to start or time to finish the 1-CSRT task versus control (Table 4; n.s.). M100907 did not alter % accuracy, % omissions, the latency to start or time to finish the 1-CSRT task versus vehicle+cocaine (Table 4; n.s.).

DISCUSSION

This study replicates and extends previous work demonstrating a role for the 5-HT_{2A}R in inherent behavioral disinhibition and demonstrates that cocaine enhances behavioral disinhibition in two distinct behavioral models of impulsive action. Treatment with the selective 5-HT_{2A}R antagonist M100907 attenuated behavioral disinhibition in the DRL-20 sec task, as evidenced by a decrease in the response rate and concomitant increase in the number of reinforcers obtained as well as a rightward shift of the IRT distribution curve. Similarly, M100907 attenuated behavioral disinhibition in the 1-CSRT task, as shown by a decrease in the number of premature responses and increase in the number of reinforcers obtained. In contrast, cocaine administration increased behavioral disinhibition in both the DRL-20 sec task (increased response rate; decreased reinforcers obtained; increased burst responding; leftward shift in the IRT distribution curve) and the 1-CSRT task (increased premature responses; decreased reinforcers obtained). M100907 moderately attenuated the cocaine-induced disruption of behavioral disinhibition in the DRL-20 sec (response rate, burst responding, peak shift) and 1-CSRT (premature responses) tasks. Thus, the 5-HT_{2A}R represents a neurobiological substrate which regulates differential facets of behavioral disinhibition as both inherent and cocaine-disrupted behavioral disinhibition are responsive to pharmacological antagonism of the 5-HT_{2A}R.

A vast literature links alterations in 5-HT function and impulsivity (for review, see Pattij & Vanderschuren 2008); however, the neurobiological mechanisms through which 5-HT regulates impulsivity are inconclusive, most likely due to the complex nature of the 5-HT system. The actions of 5-HT are mediated through 14 receptor family subtypes with its actions at the 5-HT_2R family (*e.g.*, 5-HT_{2A}R, 5-HT_{2C}R) being the most widely studied in relation to impulsive action. There is considerable evidence that inhibition of 5-HT_{2A}R-mediated transmission through either pharmacological or gene deletion techniques attenuates inherent behavioral disinhibition (present study; Winstanley *et al.* 2003, 2004a,b, 2006a; Harrison *et al.* 1997; Higgins *et al.* 2003; Fletcher *et al.* 2007, 2009; Robinson *et al.* 2008). M100907 is one of the most selective 5-HT_{2A}R antagonists available for preclinical studies (Bubar & Cunningham 2008) with 100-fold selectivity for the 5-HT_{2A}R ($K_i = 0.85$ nM) over the homologous 5-HT_{2C}R ($K_i = 88$ nM) (Kehne *et al.* 1996). Low doses of M100907 similar to those employed in this study have been shown to preferentially inhibit the effects of preferential 5-HT_{2A}R agonists (McCreary *et al.* 2003; Hitchcock *et al.* 1997; Wettstein *et al.* 1999; Gresch *et al.* 2007), but not selective 5-HT_{2C}R agonists (Dekeyne *et al.* 1999; Vickers *et al.* 2001), suggesting a selective, functional antagonism of the 5-HT_{2A}R at the doses chosen here (Nic Dhonnchadha *et al.* 2009; Dekeyne *et al.* 1999; McCreary *et al.* 2003; Gresch *et al.* 2007; Hitchcock *et al.* 1997). In accordance with the aforementioned studies, M100907 potently diminished behavioral disinhibition (present study) in both the

DRL-20 sec and 1-CSRT tasks, and this was not associated with alterations in additional measures of executive function (*e.g.*, attention, motivation, the latency to start or time to finish the 1-CSRT task), indicating that M100907 does not alter the performance of the tasks and supporting a role for tonic activation of the 5-HT_{2A}R to attune inherent levels of impulse control.

The limbic-corticostriatal circuit may be an important site of action for the 5-HT_{2A}R to modulate impulsivity (Pompeiano *et al.* 1994; Bubar & Cunningham 2008). Extensive lines of evidence implicate serotonergic mechanisms within this circuit in behavioral disinhibition (Winstanley *et al.* 2006a; Pattij & Vanderschuren 2008; Robinson *et al.* 2008). A positive correlation between 5-HT release in the mPFC and increased premature responding on the 1-CSRT task has been reported (Dalley *et al.* 2002). In addition, intra-prefrontal cortex and intra-accumbens administration of M100907 decreased impulsive responding in the 5-CSRT task (Winstanley *et al.* 2003; Robinson *et al.* 2008). These data indicate that disruption of the tonic level of activation of the 5-HT_{2A}R within the limbic-corticostriatal circuit plays a key role in impulsivity. The 5-HT_{2A}R expressed within the limbic-corticostriatal circuit serves to modulate dopaminergic (Broderick *et al.* 2004; Auclair *et al.* 2004), noradrenergic (Millan *et al.* 2000) as well as glutamatergic neurotransmission (Santana *et al.* 2004; Carli *et al.* 2006). Levels of DA and its metabolite DOPAC have been shown to rise in the mPFC of rats during performance of the 1-CSRT task, while highly impulsive rats had higher DA turnover rates in the mPFC (Dalley *et al.* 2002). Further, inhibition of α_1-noradrenoceptors, but not α_2-noradrenoceptors abates enhanced premature responding in the 5-CSRT task induced by 5-HT_{2A}R activation (Koskinen *et al.* 2003). Thus, 5-HT_{2A}R modulation of serotonergic, dopaminergic, and/or noradrenergic neurotransmission within the limbic-corticostriatal circuits may be an important mechanism by which the 5-HT_{2A}R influences impulsive behaviors (Winstanley *et al.* 2004b; Koskinen *et al.* 2003). Therefore, further exploration into the complex regulation of the 5-HT_{2A}R over 5-HT:DA:NE balance within the corticolimbic circuit as it relates to impulsivity is imperative to elucidate the utility of 5-HT_{2A}R ligands (*e.g.*, antagonists, inverse agonists) as treatments for disorders characterized by impulse control deficits *(e.g.*, drug abuse, eating disorders, *etc*.).

Impulsivity is a complex, non-unitary construct that is associated with cocaine abuse and dependence (Evenden 1999; Moeller *et al.* 2001b). In the current study, acute cocaine administration produced the hypothesized effects on behavioral disinhibition; that is, acute cocaine treatment enhanced behavioral disinhibition as measured by both the DRL-20 sec and 1-CSRT tasks. Acute cocaine treatment has previously been reported to increase impulsive action as measured in the Go/No-go task (Paine *et al.* 2003; Paine & Olmstead 2004), and premature responding in the DRL task (present study; Wenger & Wright 1990; Woolverton *et al.* 1978; Stoffel & Cunningham 2008; Wang *et al.* 2001). Further, acute administration of cocaine disrupted executive function as evidenced by a decrease in accuracy and increase in both omissions and premature responding in the 5-CSRT task (Winstanley *et al.* 2007). In the present study, cocaine did not alter accuracy or motivation in the 1-CSRT task, underscoring the utility of the 1-CSRT task to selectively measure behavioral disinhibition independent from effects on visuospatial processes (Dalley *et al.* 2002).

The apparent effectiveness of the selective 5-HT_{2A}R antagonist M100907 to suppress inherent behavioral disinhibition is greater than its effectiveness to suppress cocaine-evoked behavioral disinhibition. The dose-dependent effects of M100907 to suppress behavioral disinhibition appear in a narrow dose range (0.01–0.1 mg/kg) and are limited to certain aspects of behavioral disinhibition. The diminished effects of M100907 at the higher doses may be due to a loss of selectivity for the 5-HT_{2A}R and may reflect combined actions of M100907 at both the 5-HT_{2A}R and 5-HT_{2C}R, which tend to have oppositional effects upon

steady-state and/or cocaine-evoked behaviors (Bubar & Cunningham 2008). The dose of cocaine (10 mg/kg) employed in this study was previously demonstrated to evoke maximal behavioral disinhibition in the DRL-20 sec task (Stoffel & Cunningham 2008), but did not produce maximal disruption of behavioral disinhibition in the 5-CSRT task (Winstanley *et al.* 2007). While the present findings support a role for the 5-HT_{2A}R in cocaine-induced behavioral disinhibition, the effectiveness of M100907 is influenced by the manner in which cocaine impacts the neurochemistry involved in the generation of impulsivity. Serotonin, DA, and NE each have been implicated as mediators in multiple aspects of impulsivity (for review, see Pattij & Vanderschuren 2008). Given that this dose of cocaine would be expected to enhance synaptic levels of all three monoamines in the limbic-corticostriatal circuit (Koe 1976; Bradberry & Roth 1989; Kalivas & Duffy 1990; Broderick *et al.* 2004; Bubar *et al.* 2003), blockade of 5-HT_{2A}R stimulation consequent to cocaine-evoked 5-HT release (Broderick *et al.* 2004) might be expected to modulate only the specific components of impulsivity related to the 5-HT_{2A}R such as the response rate, burst responding, and/or the number of premature responses. Thus, additional aspects of enhanced impulsive behavior observed following cocaine administration are most likely mediated by monoamine neurotransmission that is not solely modulated by the 5-HT_{2A}R and may likely be determined by the balance of function at multiple 5-HT_2R subtypes (*e.g.*, 5-HT_{2C}R) (Fletcher *et al.* 2007), DA receptors (*e.g.*, D1-like, D2-like) (van Gaalen *et al.* 2006; Koskinen & Sirvio 2001; Passetti *et al.* 2003), and/or NE receptors (*e.g.*, α_1 NE) (Koskinen *et al.* 2003).

From a translational perspective, cocaine-dependent subjects often present with both impulsivity (Moeller *et al.* 2001b, 2002, 2004) and high levels of reactivity to cocaine-associated cues (O'Brien *et al.* 1998; Carter & Tiffany 1999; Modesto-Lowe & Kranzler 1999), and studies in amphetamine-treated rats suggest that impulsivity and cue reactivity may be intertwined (Cardinal *et al.* 2000), thereby adding an additional layer of complexity to the relationship between cocaine exposure and impulsivity. Data from the current study and previous studies investigating the incentive motivational aspects of cocaine-associated cues (Nic Dhonnchadha *et al.* 2009) suggest that the 5-HT_{2A}R serves as a functional rheostat over both impulsive behavior and cue reactivity. Thus, the 5-HT_{2A}R may represent a promising pharmacotherapeutic for cocaine dependence in which impulsivity is a core trait (Moeller *et al.* 2001b) and a selective 5-HT_{2A}R antagonist may help to prevent relapse and promote abstinence in cocaine-dependent individuals by reducing impulsivity and cue-reactivity.

In conclusion, M100907 attenuated inherent levels of behavioral disinhibition in two distinct animal models and is effective at reducing specific aspects of cocaine-evoked disruption of behavioral disinhibition in rats, indicating a key role for the 5-HT_{2A}R in maintaining the balance of monoaminergic interactions underlying impulsivity. As a whole, the results from this study and others suggest that the loss of impulse control is most likely a combination of, and complex interaction between, the multiple phenotypic facets of impulsivity under the influence of the 5-HT_{2A}R system. A greater understanding of the 5-HT:DA:NE etiology of impulse control disorders associated with cocaine use and the benefits of intervention strategies that normalize the balance within 5-HT_2R systems may reveal ways to devise more personalized therapeutics based on levels of impulsivity in cocaine-dependent patients.

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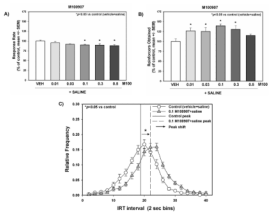

Figure 1. The effects of M100907 administration on behavioral disinhibition measured with the DRL-20 sec task

Response rate **(A)** and number of reinforcers (0.25 sec water deliveries) obtained **(B)** on the DRL-20 s task test day are presented as % of control (vehicle+saline) (mean ± SEM). **(C)** The relative frequency (frequency of inter-response time/total number of responses ± SEM) of a given inter-response interval for control and M100907 (0.1 mg.kg) is represented as a single point for each 2-s time bin. M100907 (0.01, 0.03, 0.1, 0.3, 0.5 mg/kg) was administered 15 min prior to saline injections; vehicle (1 mL/kg saline or 1% Tween 80) was administered immediately before DRL-20 sec task test sessions in a counterbalanced within-subjects design. "→" Represents the peak shift for 0.1 mg/kg M100907 versus the control peak relative frequency. Statistical comparisons of descriptive statistics for the inter-response time distributions can be found in Table 1. **p*<0.05 vs. control ^*p*<0.05 vs. vehicle +cocaine (one way repeated measures ANOVA with Dunnett's procedure)

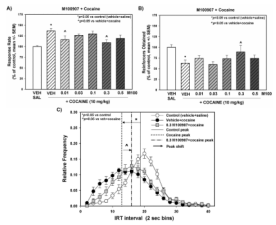

Figure 2. The effects of M100907 in combination with cocaine administration on behavioral disinhibition measured with the DRL-20 sec task

Response rate (**A**) and number of reinforcers (0.25 sec water deliveries) obtained (**B**) on the DRL-20 s task test day are presented as % of control (vehicle+saline) treatment (mean ± SEM). (**C**) The relative frequency (frequency of inter-response time/total number of responses ± SEM) of a given inter-response interval for control and cocaine alone or M100907 (0.3 mg/kg) + cocaine is represented as a single point for each 2-s time bin. M100907 (0.01, 0.03, 0.1, 0.3, 0.5 mg/kg) was administered 15 min prior to vehicle or cocaine injections; vehicle (1 mL/kg saline or 1% Tween 80) or cocaine (10 mg/kg) was administered immediately before DRL-20 sec task test sessions in a counterbalanced within-subjects design. "←" Represents the peak shift for cocaine versus the control peak relative frequency; "→" represents the peak shift for 0.3 mg/kg M100907 + cocaine versus cocaine peak relative frequency. Statistical comparisons of descriptive statistics for the inter-response time distributions can be found in Table 2. *p<0.05 vs. control ^p<0.05 vs. vehicle +cocaine (one way repeated measures ANOVA with Dunnett's procedure)

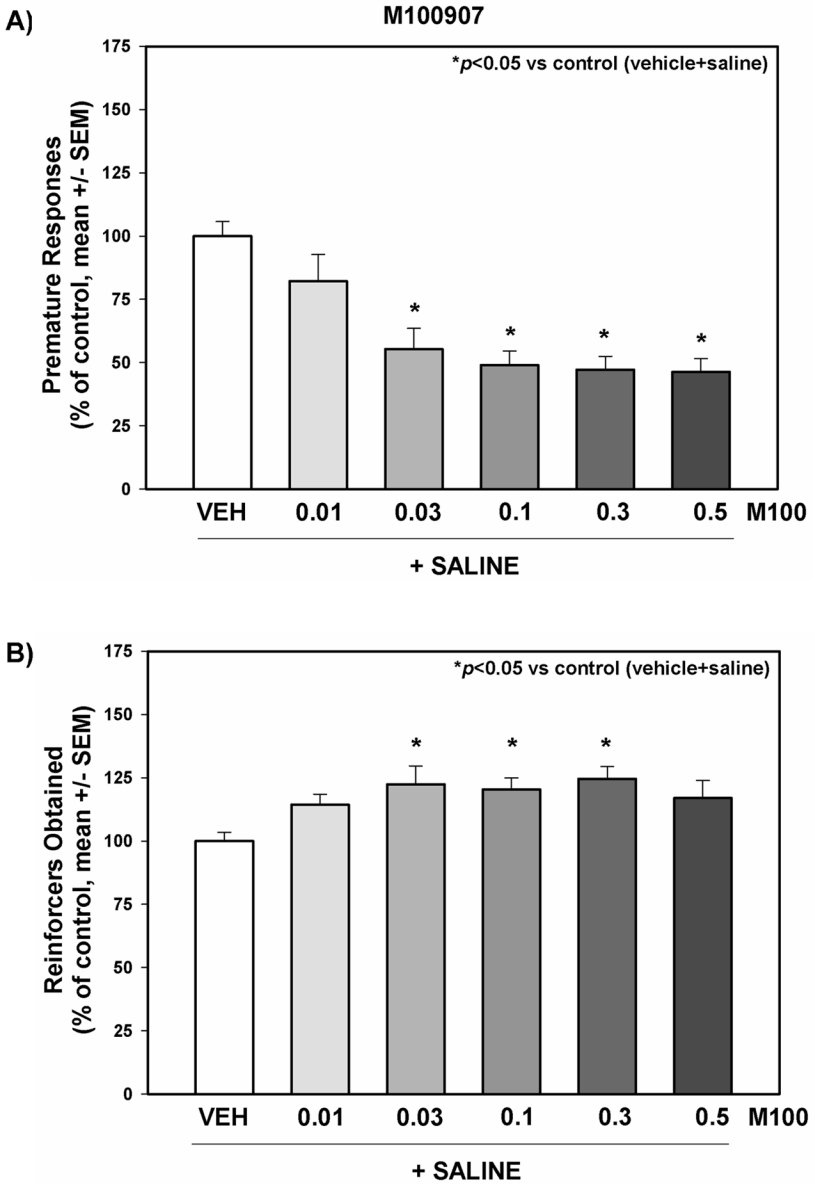

Figure 3. The effects of M100907 administration on behavioral disinhibition measured with the 1-CSRT task

Premature responses **(A)** and reinforcers obtained **(B)** on the 1-CSRT task test day are presented as % of control (vehicle+saline) treatment (mean + SEM). M100907 (0.01, 0.03, 0.1, 0.3, 0.5 mg/kg) was administered 15 min prior to saline injections; vehicle (1 mL/kg saline or 1% Tween 80) was administered immediately before 1-CSRT task test sessions in a counterbalanced within-subjects design. *p<0.05 vs. control ^p<0.05 vs. vehicle+cocaine (one way repeated measures ANOVA with Dunnett's procedure)

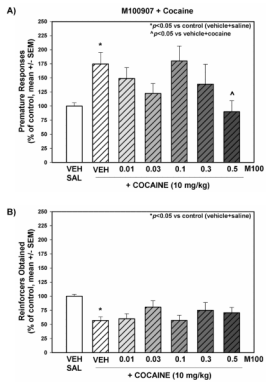

Figure 4. The effects of M100907 in combination with cocaine administration on behavioral disinhibition measured with the 1-CSRT task

Premature responses (**A**) and reinforcers obtained (**B**) on the 1-CSRT task test day are presented as % of control (vehicle+saline) treatment (mean + SEM). M100907 (0.01, 0.03, 0.1, 0.3, 0.5 mg/kg) was administered 15 min prior to vehicle or cocaine injections; vehicle (1 mL/kg saline or 1% Tween 80) or cocaine (10 mg/kg) was administered immediately before 1-CSRT task test sessions in a counterbalanced within-subjects design. *p<0.05 vs. control ^p<0.05 vs. vehicle+cocaine (one way repeated measures ANOVA with Dunnett's procedure)

Table 1

IRT distribution descriptive statistics for **M100907** administration.

		IRT descriptive statistics (mean ± SEM)		
M100907 Pretreatment	***Treatment***	**Mean**	**Median**	**Mode**
Vehicle	Saline	19.06 ± 0.69	18.56 ± 0.64	18.81 ± 0.87
0.01 mg/kg	Saline	20.58 ± 0.55	20.25 ± 0.53	20.50 ± 0.85
0.03 mg/kg	Saline	21.50 ± 0.78	21.06 ± 0.75	20.63 ± 1.31
0.1 mg/kg	Saline	**22.48 ± 0.82***	**21.72 ± 0.49***	**21.94 ± 0.61***
0.3 mg/kg	Saline	20.52 ± 1.21	20.00 ± 0.91	19.88 ± 1.09
0.5 mg/kg	Saline	22.54 ± 1.59	**21.63 ± 1.16***	20.50 ± 1.12

* $p<0.05$ vs. control (vehicle+saline)

Table 2

IRT distribution descriptive statistics for **M100907 + Cocaine (10 mg/kg)** administration.

		IRT descriptive statistics (mean ± SEM)		
M100907 Pretreatment	***Treatment***	**Mean**	**Median**	**Mode**
Vehicle	Saline	19.06 ± 0.69	18.56 ± 0.64	18.81 ± 0.87
Vehicle	Cocaine	**14.49 ± 0.72***	**13.81 ± 0.73***	**12.88 ± 1.58***
0.01 mg/kg	Cocaine	17.14 ± 2.04	15.50 ± 1.22	12.38 ± 1.69
0.03 mg/kg	Cocaine	16.28 ± 0.85	16.25 ± 0.98	16.13 ± 1.43
0.1 mg/kg	Cocaine	15.60 ± 0.88	14.94 ± 0.95	11.69 ± 1.52
0.3 mg/kg	Cocaine	17.06 ± 0.97	16.50 ± 0.94	16.00 ± 0.82
0.5 mg/kg	Cocaine	16.57 ± 1.25	15.88 ± 1.39	14.25 ± 2.05

* $p<0.05$ vs. control (vehicle+saline)

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Table 3

1-CSRT descriptive statistics for **M100907** administration.

		1-CSRT task descriptive statistics (mean ± SEM)			
M100907 Pretreatment	***Treatment***	**% Accuracy**	**% Omissions**	**Latency to Start (sec)**	**Time to Finish (sec)**
Vehicle	Saline	100 ± 0.27	4.31 ± 0.45	2.63 ± 0.79	926.60 ± 27.52
0.01 mg/kg	Saline	100.82 ± 0.52	4.08 ± 1.32	0.63 ± 0.26	888.25 ± 22.91
0.03 mg/kg	Saline	99.58 ± 0.55	4.95 ± 1.45	4.13 ± 3.70	1016.50 ± 109.59
0.1 mg/kg	Saline	100.23 ± 1.05	7.05 ± 2.55	1.38 ± 0.84	990.38 ± 55.66
0.3 mg/kg	Saline	99.98 ± 0.42	6.56 ± 1.72	1.50 ± 1.36	1077.00 ± 77.26
0.5 mg/kg	Saline	100.83 ± 0.68	3.80 ± 1.65	0.25 ± 0.16	964.63 ± 55.56

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Table 4

1-CSRT descriptive statistics for **M100907 + Cocaine (10 mg/kg)** administration.

		1-CSRT task descriptive statistics (mean ± SEM)			
M100907 Pretreatment	***Treatment***	**% Accuracy**	**% Omissions**	**Latency to Start (sec)**	**Time to Finish (sec)**
Vehicle	Saline	100 ± 0.27	4.45 ± 0.41	2.63 ± 0.79	926.60 ± 27.52
Vehicle	Cocaine	98.90 ± 0.54	9.65 ± 1.66	1.38 ± 1.12	1103.38 ± 126.54
0.01 mg/kg	Cocaine	99.55 ± 1.19	12.13 ± 4.90	2.88 ± 1.48	1242.50 ± 278.08
0.03 mg/kg	Cocaine	98.31 ± 0.87	6.08 ± 1.00	1.38 ± 0.53	1402.25 ± 202.26
0.1 mg/kg	Cocaine	97.30 ± 1.87	9.05 ± 2.44	2.13 ± 1.43	1257.25 ± 254.97
0.3 mg/kg	Cocaine	98.59 ± 1.00	5.12 ± 1.50	1.17 ± 0.65	1447.13 ± 315.85
0.5 mg/kg	Cocaine	100.29 ± 0.68	14.85 ± 5.66	1.00 ± 0.50	1453.63 ± 247.75