

The Roles of Central Amygdala D1 and D2 Receptors on Attentional Performance in a Five-Choice Task

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The central amygdala (CeA) has been shown to play an important role in mediating several attentional processes, including selective and sustained attention. Emerging evidence suggests that the connections between the CeA and the midbrain dopamine areas are important for attentional processing. However, little is known about the role of dopaminergic input into the CeA in mediating attentional processes. To investigate how dopamine activity in the CeA modulates attentional processing, CeA D1 and D2 receptors were temporarily inactivated during testing in a 5-choice task. In this task, rats were trained to detect 1 of 5 recessed ports that briefly illuminated in order to receive a food reward, therefore requiring the rats to successfully sustain their attention to monitor all 5 ports and selectively attend to the lit port. Then, rats were tested in several altered versions of the task to increase attentional load (e.g., variable ready period). In 2 experiments, the D1 antagonist CH 23390 or the D2 antagonist raclopride were infused into the bilateral CeA preceding the test sessions. D1, but not D2, inactivation reduced performance in the more demanding versions of the 5-choice task. Therefore, CeA D1 receptors might mediate attentional functions important for visual cue detection in a 5-choice task.

Keywords: central amygdala, dopamine, selective and sustained attention, 5-choice task

The central nucleus of the amygdala (CeA) plays an important role in appetitive learning and attentional processing (Holland & Gallagher, 1999). The CeA is necessary for several forms of attention, such as enhanced orienting to a conditioned stimulus (e.g., rearing toward an appetitively conditioned light stimulus; Gallagher, Graham, & Holland, 1990; McDannald, Kerfoot, Gallagher, & Holland, 2004) and enhanced attention to a conditioned stimulus as a result of an unexpected outcome contingency (Holland & Gallagher, 1993). Further, the connections between CeA and midbrain dopamine areas have been implicated in these attentional processes (El-Amamy & Holland, 2006; Han, McMahan, Holland, & Gallagher, 1997; Lee, Gallagher, & Holland, 2010; Lee et al., 2005; Lee, Wheeler, & Holland, 2011; Lee, Youn, Gallagher, & Holland, 2008; Lee, Youn, O, Gallagher, & Holland, 2006).

The CeA also modulates selective and sustained attention, as measured by the ability to attend to a specific visual cue in the presence of multiple cues. Holland, Han, and Gallagher (2000) found that bilateral CeA lesions impaired performance in an operant multiple-choice reaction time (RT) task. In this task, rats were trained to nose poke into a port that was briefly illuminated (500 ms) among three ports to receive a food reward. The impending port illumination was signaled by the houselight for 5 s. When the attentional load was increased by shortening the port illumi-

nation to 100 ms or by varying the duration of the houselight signal, rats with CeA lesions showed reduced accuracy and response time. In subsequent studies, Holland and colleagues also showed that the CeA's connections to the cholinergic substantia innominata and nucleus basalis magnocellularis (SI/nBM) and the cholinergic input to the medial prefrontal cortex (mPFC) were important for mediating the attentional performance in a similar multiple-choice reaction task (Holland, 2007; Maddux, Kerfoot, Chatterjee, & Holland, 2007).

However, it is currently unknown whether the midbrain dopamine connections with the CeA—previously implicated in enhanced attentional processing of conditioned cues (Lee et al., 2005, 2006)—also play an important role in mediating attentional performance during the multiple-choice reaction task. Anatomically, the CeA and the midbrain dopamine cells have reciprocal connections (Asan, 1997a, 1997b; Bourgeois, Gauriau, & Bernard, 2001; Cheung, Ballew, Moore, & Lookingland, 1998; Fallon, Koziell, & Moore, 1978; Fudge & Haber, 2000; Gonzales & Chesselet, 1990; Haber & Fudge, 1997; Lee et al., 2005, 2011; L. W. Swanson, 1982), suggesting that dopamine can have a direct influence on CeA function. In fact, several studies showed that manipulations of dopamine receptors in the CeA altered learning and memory in fear conditioning and conditioned place preference paradigms (Guarraci, Frohardt, Falls, & Kapp, 2000; Guarraci, Frohardt, & Kapp, 1999; Rezayof, Zarrindast, Sahraei, & Haeri-Rohani, 2002; Zarrindast, Rezayof, Sahraei, Haeri-Rohani, & Rassouli, 2003). Our recent study also suggests that dopamine function in the CeA is critical for a particular type of attentional processing (Smith, Geissler, Schallert, & Lee, 2013). Either permanent dopamine depletion or temporary blockade of D1 receptors in the CeA produced deficits in the rat's ability to disengage from an ongoing activity and attend to an incoming stimulus. Therefore, we examined whether dopamine functions in the CeA are important for

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attentional performance during a five-choice task by temporally inactivating CeA D1 receptors (Experiment 1) or CeA D2 receptors (Experiment 2).

Method

Subjects

One hundred three male Long-Evans rats (Charles River, Wilmington, MA), weighing 250 to 275 g upon arrival, were housed in a vivarium with a reversed 14:10-hr light–dark cycle with lights off at 10:00 a.m. One week after arrival, rats were food restricted to maintain 90% of their free-feeding body weight but had constant access to water. Rats were allowed ad libitum access to food and water during the 1-week recovery period after surgery. All behavioral training and testing occurred during the dark phase. All experiments were conducted according to the [National Institutes of Health's \(1986\) Guide for the Care and Use of Laboratory Animals](#), and all protocols were approved by the Institutional Animal Care and Use Committee at The University of Texas at Austin.

Surgery

Rats were anesthetized using 2% to 5% isoflurane gas (Abbott Laboratories, Abbott Park, IL) and were placed into the stereotaxic frame (Kopf Instruments, Tujunga, CA). All rats were implanted with bilateral guide cannulas (26 gauge, PlasticsOne, Roanoke, VA) to target the CeA ($AP = -2.0$, $ML = \pm 3.6$, $DV = -7.2$). Once the cannulas were in place, dental acrylic (Lang Dental Manufacturing Co., Wheeling, IL) was poured onto the skull to create a headcap with four jewel-screws anchored to the skull. After the dental acrylic had completely dried, dummy cannulas were inserted into the guide cannulas. The rats received a subcutaneous injection of buprenorphine hydrochloride (0.01 mg/kg; TW Medical, Denver, CO) and were given 1 week to recover from surgery.

Apparatus

Five-choice training and testing was conducted in eight operant boxes with aluminum side walls and ceiling, and clear acrylic front and back walls (30.5 cm W $\times$ 25.4 cm D $\times$ 30.5 cm H; Coulbourn Instruments, Whitehall, PA). One of these side walls was concave and contained five recessed ports (each 2.5 cm in diameter), with each of the recessed ports 3 cm from the grid floor (stainless steel rods 0.5 cm in diameter, parallel, spaced 1.0 cm apart), and had three red LED lights inside to illuminate the port at the appropriate time. Additionally, the ports were equipped with infrared beams that detected nose pokes. Opposite the concave wall was a 2-W houselight (centered on the wall, 26 cm from the floor) and a recessed food cup (centered, 2 cm from the floor) equipped with an infrared beam to detect entries. On the top of the box was an activity monitor (Coulbourn Instruments) that measured activity through infrared beam breaks. Each box was housed in a light- and sound-attenuating chamber (58.4 cm $\times$ 61 cm $\times$ 45.7 cm; Coulbourn Instruments) and interfaced with a computer using GraphiState 3.1 (Coulbourn Instruments).

Five-Choice Task

Shaping. To train the rats on the five-choice task, two shaping procedures were conducted. First, rats underwent a magazine-shaping session in which they were trained to eat a single grain pellet (45-mg grain tablet; Test Diet, Richmond IN) delivered to a food cup located within the conditioning chamber. A total of 30 pellets were delivered at a variable interval (averaging 60 s) over a 30-min session. After this session, all rats reliably retrieved grain pellets from the food cup. Second, the rats went through a nose-poke-shaping session in which they were trained to make a nose-poke response to the ports. All five ports were illuminated for 30 s, and a nose poke to any port during this time resulted in the delivery of a grain pellet in the food cup. This daily session was continued until the rats met criterion of 80% or more responses over 30 trials, with a variable intertrial interval (intertribal interval [ITI]) of 30 s. After completing the shaping sessions, the rats began training in the five-choice task.

Training. Rats were trained to the baseline task gradually. The beginning of a trial was signaled by the houselight. After 5 s of constant illumination (i.e., ready period), one of the five target ports was illuminated. Rats first had to detect (i.e., nose poke) a port that was illuminated for 30 s. Once the rats reached the criterion (80% trials with correct responses), the portlight duration was shortened successively to 20 s, 10 s, 5 s, 3 s, 1 s, and then, finally, to 500 ms once they met the criterion at each stage. Regardless of the portlight duration, the session time was 30 min, but as portlight duration decreased, the number of trials increased to accommodate the 30 min training window. Therefore, the total trials for each stage ranged from 30 trials (for 30-s portlight) to 60 trials (for 500-ms portlight). The rats had a total of 5 s (i.e., response period) from the time the portlight was illuminated to make a nose-poke response to the target port, unless the portlight duration was longer than 5 s, in which case the rats were allowed to make a nose poke for the entire duration the port was illuminated. A correct nose poke resulted in an immediate delivery of a grain pellet and darkening of the houselight (and the portlight if still illuminated). If no correct response was made during the 5-s response period, the houselight was darkened. Responses to the nontarget ports (i.e., the other four that were not illuminated) during the 5-s response period were recorded as errors but resulted in no consequences. In addition, nose-poke responses to any of the five ports during the 5-s ready period were recorded as premature responses but did not have any consequences. The baseline task consisted of 60 trials in a 30-min session (variable ITI of 30 s), and each port was illuminated equally (i.e., 12 times per session) on a semirandom schedule (i.e., no port was lit more than two times consecutively). This procedure was adapted from Holland and colleagues (Holland, 2007; Holland et al., 2000; Maddux et al., 2007), which differs from the typical 5-choice serial RT task (5CSRTT) procedure (Robbins, 2002). The initiation and termination of the trials are independent of the rats' response in our procedure. Therefore, premature response during the ready period does not delay or cancel port illumination. In addition, an incorrect response during the response period does not terminate the trial, allowing the rats an opportunity to correct their mistakes and make a correct response. Nevertheless, this modified version of the five-choice task was sensitive to attentional challenges and manipulations of the CeA and its connections to the cortico cholin-

ergic system (Holland, 2007; Holland et al., 2000; Maddux et al., 2007)

To finish training on the 500-ms baseline task, the rats had to reach the criterion twice during 3 consecutive training days. Then, the rats received bilateral cannulas implantation, were given a week to recover, and were retrained on the 500-ms task to the same criterion as before (see Table 1).

Testing. Once rats reached criterion on the 500-ms task post-surgery, they received a handling procedure for 2 days before testing. The handling procedure consisted of a mock drug infusion process in which the dummy cannulas were removed, the rats were gently held for a couple of minutes, and the dummy cannulas were replaced. The testing phase was 7 days long, with 4 infusion test days. These infusion tests consisted of one baseline test and three challenge tests (all 60 trials each). In the first challenge, the portlight duration was shortened from 500 to 100 ms for all trials. In the second challenge, the typically constant 5-s ready period varied to 1, 5, or 9 s. The third challenge was a blink condition in which the houselight blinked during the 5-s ready period. Half of the rats were run in the order as follows: 500-ms baseline task, shortened portlight challenge, variable ready period challenge, and blink challenge. The other half were run in the reverse order (blink, variable ready period, shortened portlight, and baseline). In between these 4 test days, the rats underwent the baseline task with no infusion to ensure that there were no lasting effects of the drugs (see Table 2).

Infusions

Rats were assigned to receive 0.9% saline (Experiments 1 and 2), a D1 antagonist SCH23390 (Sigma Aldrich, St Louis, MO; Experiment 1), or a D2 antagonist raclopride (Sigma Aldrich; Experiment 2). All the infusions were given 15 min before the start of testing. Bilateral infusions (0.2 µl each) were delivered over 2 min via 33-gauge infusion needle (PlasticsOne) that extended 1 mm beyond the guide cannula using an infusion pump (Harvard Apparatus, Holliston, MA) and a Hamilton syringe (Hamilton, Reno, NV). Two doses of SCH 23390 (0.5 µg and 1.0 µg given bilaterally) and two doses of raclopride (0.25 µg and 0.75 µg given bilaterally) were used. Therefore, there were three groups per experiment: (a) saline, SCH 23390 0.5 µg, SCH23390 1.0 µg; (b) saline, raclopride 0.25 µg, and raclopride 0.75 µg.

Histology

After behavioral testing was complete, rats were perfused transcardially with 0.9% saline and 10% formalin. The brains were

extracted, placed into 20% sucrose formalin solution overnight, and then frozen the following day. Brains were sliced using a sliding microtome at a thickness of 40 µm and sections containing the CeA were saved. Every fourth section was mounted and Nissl-stained to verify cannula placements. Cannulas were considered to have good placements if the guide cannula track was visualized within 1 mm above the CeA (as defined by Swanson, 2003) as the infusion cannula extended 1 mm past the tip of the guide cannula, or if the injection needle track was seen within the CeA.

Statistical Analyses

All statistical analyses were conducted in PASW version 18 (formerly SPSS, Inc., Hong Kong). All measures of performance in the task were assessed using a repeated measures 3 × 4 analysis of variance (ANOVA), with the between-group factor of drug assignment (control and two different doses of drugs) and the within factors of testing sessions (baseline and three different attentional challenges). Four post hoc one-way ANOVAs were conducted (when appropriate) on each testing session, with a between-group factor of drug assignment.

Results

Experiment 1: CeA D1 Antagonism

Cannula placement verification. Cannula placements were considered acceptable if the guide cannula track was visualized within the CeA or up to 1 mm above the CeA (as defined by L. W. Swanson, 2003). The number of rats with acceptable cannula placements was 10 in the saline control condition, eight in the SCH 23390 1.0-µg group, and six in the SCH 23390 0.5-µg group (see Figure 1). Six rats in the saline group included in the analyses only had acceptable unilateral cannula placements. However, their performance levels were not different from the ones with acceptable bilateral placements at all four tests with saline infusions (all *ps* > 0.1). Unacceptable placements were either too dorsal or too rostral in relation to the CeA and located in the striatum, substantia innominata, or the intercalated nucleus. Additionally, one of the rats in the saline group with acceptable unilateral placements received a mock infusion prior to testing (because of blocked cannula), in which the rat was gently held on the experimenter's lap for the duration of the actual infusion.

Postsurgery training. Rats were retrained daily on the baseline 500-ms task postsurgery until they met the criterion of 80% correct performance (i.e., trials with correct nose poke to the target port) twice within 3 consecutive days of training. To determine whether there were any preexisting differences between the groups prior to drug infusions, two measures were examined: (a) the average percent correct trials on the days the rats met criterion, and (b) the number of days necessary to meet criterion. When a one-way ANOVA was run on average percent correct trials, there was a main effect of group, *F*(2, 21) = 4.34, *p* = .026. Post hoc Tukey's HS revealed that the average percent correct trials for the SCH 23390 1.0-µg group (*M* = 88.85, *SEM* = 1.03) was significantly higher than the control group (*M* = 84.16, *SEM* = 0.97). However, when a one-way ANOVA was run on the amount of

Table 1
Experiment Progression

Event	Number of days	Criterion to progress
Presurgery training	10–14	≥80% correct trials 2 of 3 consecutive days
Surgery and recovery	7	n/a
Postsurgery training	2–10	≥80% correct trials 2 of 3 consecutive days
Testing	7	No criterion—rats moved through testing schedule regardless of performance

Table 2
Five-Choice Testing Procedure

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Order 1	<i>500 msec</i>	Baseline	<i>100 msec</i>	Baseline	<i>Variable</i>	Baseline	<i>Blink</i>
Order 2	<i>Blink</i>	Baseline	<i>Variable</i>	Baseline	<i>100 msec</i>	Baseline	<i>500 msec</i>

Note. Rats received infusions every other day starting day 1 (bold italic) and received no infusion on three baseline days interspersed between infusion days.

training days needed to reach criterion, there was no difference between groups, $F(2, 21) = 1.15$, $p = .34$.

Infusion tests.

Accuracy. Accuracy in each test was measured as percentage of trials with correct responses out of a total 60 trials (Figure 2A). The results show an overall main effect of drug, $F(2, 21) = 6.598$, $p = .006$, and an interaction of the drug and testing, $F(6, 63) = 3.389$, $p = .006$, whereas the overall testing effect was marginally significant, $F(3, 63) = 2.537$, $p = .065$. To further examine the interaction, separate one-way ANOVAs were conducted for each testing session. These revealed that the D1 antagonist SCH 23390 had no effect on performance in the 500-ms baseline test, $F(2, 21) = 0.645$, $p = .54$, or in the 100-ms test, $F(2, 21) = 1.087$,

$p = .36$. However, D1 receptor antagonism did impact performance at the variable ready period test, $F(2, 21) = 4.539$, $p = .02$, in which the higher dose of SCH 23390 (1.0 μg) significantly lowered accuracy compared with the control group (Tukey's HSD). In the blinking houselight challenge, there was also a significant effect of group assignment, $F(2, 21) = 9.661$, $p = .001$, with the rats receiving the higher dose of SCH 23390 displaying reduced accuracy compared with control rats and rats receiving the lower dose of SCH 23390.

Correct response latency. Performance in the five-choice task was also assessed using latency to respond correctly (Figure 2B). The overall results show a main effect of testing, $F(3, 63) = 4.354$, $p = .008$, a trend of a main effect of drug, $F(2, 21) = 3.325$, $p = .056$, and a significant interaction of testing and drug, $F(6, 63) = 2.84$, $p = .016$. Further analyses revealed that SCH 23390 had no effect on response latency in the 500-ms test, $F(2, 21) = 0.175$, $p = .84$, the 100-ms test, $F(2, 21) = 0.177$, $p = .84$, or the variable ready period test, $F(2, 21) = 1.771$, $p = .20$. However, the D1 antagonist did have an effect on response latency in the blinking houselight challenge, $F(2, 21) = 11.673$, $p < .001$, in which the rats receiving the higher dose of SCH 23390 were slower to respond correctly than the rats receiving the lower dose or saline.

Omissions. Omissions were defined as trials in which no nose-poke response (correct or incorrect) to the ports was made during the 5-s response period (Figure 2C). The data show a main effect of testing, $F(3, 63) = 3.128$, $p = .032$, a main effect of drug, $F(2, 21) = 12.516$, $p < .001$, and an interaction of testing and drug, $F(6, 63) = 2.904$, $p = .015$. One-way ANOVAs revealed that there was a main effect of drug in all three attentional challenges (100 ms, $F[2, 21] = 6.81$, $p = .005$; variable ready period, $F[2, 21] = 4.782$, $p = .019$; blink, $F[2, 21] = 8.373$, $p = .002$), but not in the 500-ms task, $F(2, 21) = 0.692$, $p = .512$ (Figure 2C). Tukey's post hoc tests demonstrated that at all attentional challenges, rats receiving the higher dose of SCH 23390 had a higher rate of omissions than the other two groups.

Premature responses. Premature responses were defined as nose-poke responses to the ports during the ready period prior to the illumination of a port (Figure 2D). There was a main effect of testing, $F(3, 63) = 19.832$, $p < .001$, a main effect of drug, $F(2, 21) = 6.302$, $p = .007$, and an interaction of testing and drug, $F(6, 63) = 3.741$, $p = .003$. Further analyses elucidated that there was a main effect of drug at all attentional challenges (100 ms, $F[2, 21] = 4.414$, $p = .025$; variable, $F[2, 21] = 6.757$, $p = .005$; blink, $F[2, 21] = 8.487$, $p = .002$), but not at the 500-ms task, $F(2, 21) = 2.436$, $p = .112$. Rats receiving the higher dose of SCH 23390 committed fewer premature responses compared with control rats at all three attentional challenges, as well as fewer premature responses compared with rats receiving the lower dose of SCH 23390 in the blink condition.

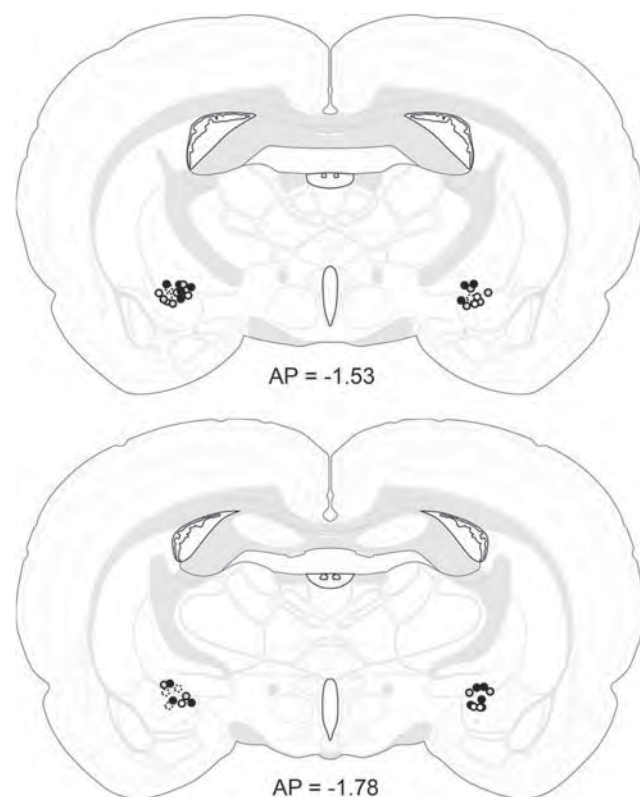


Figure 1. Cannula placements within the central amygdala between AP -1.53 and -2.00 . Each oval represents a guide cannula tip at its most central point for each animal. Filled ovals represent the animals receiving SCH 23390, with the gray representing the lower dose (0.5 μg) and the black representing the higher dose (1.0 μg); open (white) ovals represent animals in the control group; dotted ovals represent the placements of rats with unilaterally acceptable placements.

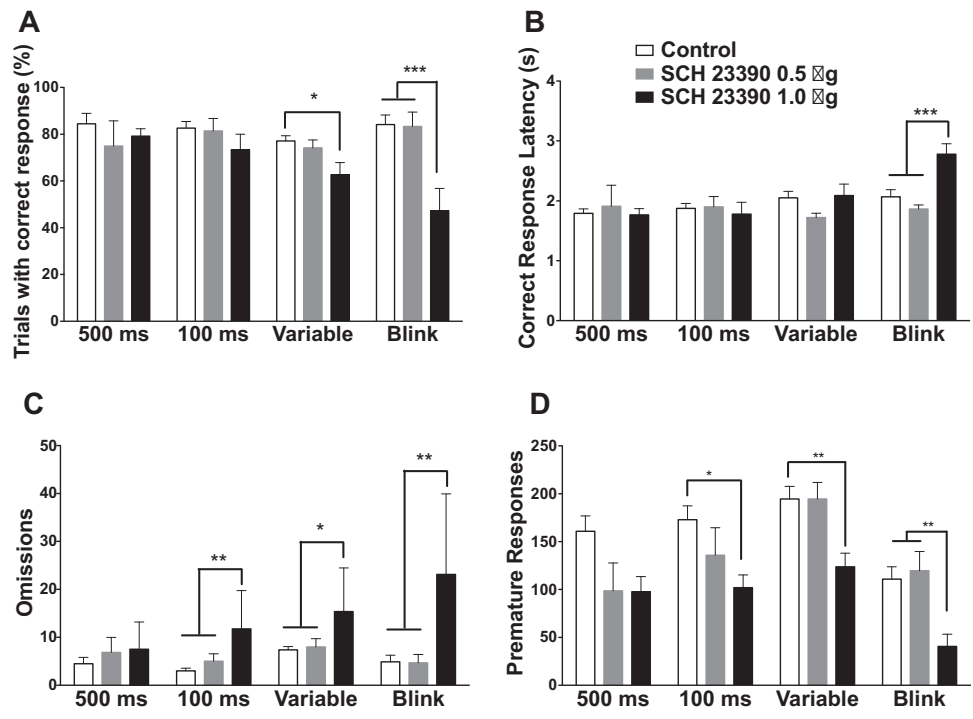


Figure 2. (A) Mean ($\pm$ SEM) percent trials with correct responses across all tests. (B) Mean ($\pm$ SEM) latency to make the first correct response. (C) Mean ($\pm$ SEM) numbers of trials with omissions (no nose pokes during the response time) across all tests. (D) Mean ($\pm$ SEM) numbers of premature responses across all tests. Premature responses were defined as nose pokes to any ports during the ready period directly prior to the portlight illumination. * $p < .05$. ** $p < .01$. *** $p < .001$.

Locomotor activity. To quantify locomotor activity during testing sessions, beam breaks from an infrared activity monitor were recorded for the duration the rats were in the operant boxes. Locomotor activity (seen in Table 3) was not affected by the application of a D1 antagonist as demonstrated by a lack of significant main effect of drug, $F(2, 21) = 0.893, p = .424$, as well as no main effect of testing, $F(3, 63) = 0.861, p = .466$, or interaction of the two factors, $F(6, 63) = 1.45, p = .21$. The results eliminate the possibility of motor impairment as an explanation for the decrements in performance seen in the attentional challenges. Furthermore, we analyzed the latency to retrieve the food pellets once the rats made the correct nose-poke response (see Table 3). There were no differences among the groups at any testing point: drug, $F(2, 21) = 0.53, p = .535$, testing, $F(3, 63) = 0.454, p = .715$, or the interaction, $F(6, 63) = 0.905, p = .497$. These results further rule out motor, as

well as motivational, factors for the decreased performance observed in the attentional challenges.

Experiment 2: CeA D2 Antagonism

Cannula placement verification. Cannula placements were again considered acceptable if the cannula track was visualized within the CeA or up to 1 mm above the CeA (see Figure 3). In Experiment 2, the number of rats with acceptable placements was six in the control condition, seven in the raclopride 0.25-µg group, and six in the raclopride 0.75-µg group. Four of the rats in the saline group only had acceptable unilateral cannula placements. Unacceptable cannula placements were located dorsal to the CeA in the striatum or rostral to the CeA in the striatum or substantia innominata. Additionally, two of these four rats only received a mock infusion because of blocked guide cannulas.

Table 3
Locomotor Activity and Food Cup Latency in Experiment 1 (D1 Receptor Antagonism)

	Group	500 ms	100 ms	Variable	Blink
Activity (no. of beam breaks)	Saline	491 $\pm$ 91.60	525.3 $\pm$ 73.75	419 $\pm$ 84.14	467.7 $\pm$ 70.04
	SCH 0.5 µg	446 $\pm$ 96.43	525.33 $\pm$ 94.54	544.67 $\pm$ 125.28	676.67 $\pm$ 135.67
	SCH 1.0 µg	393.5 $\pm$ 52.15	416.75 $\pm$ 94.14	462.42 $\pm$ 60.74	377.63 $\pm$ 54.66
Food cup latency (s)	Saline	1.55 $\pm$.24	1.28 $\pm$.07	1.40 $\pm$.18	1.45 $\pm$.245
	SCH 0.5 µg	1.67 $\pm$.12	1.74 $\pm$.24	1.67 $\pm$.19	1.67 $\pm$.14
	SCH 1.0 µg	1.52 $\pm$.11	1.49 $\pm$.12	1.55 $\pm$.10	1.52 $\pm$.11

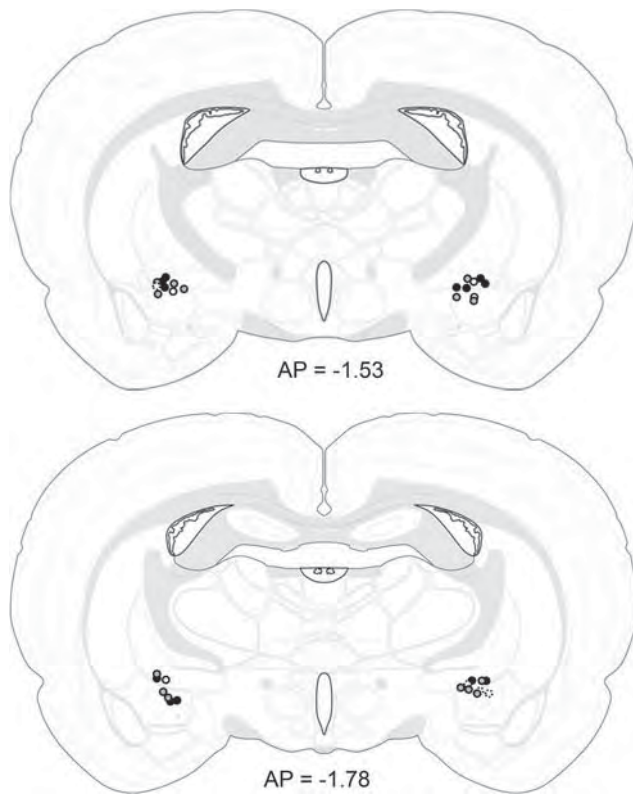


Figure 3. Cannula placements within the central amygdala between AP -1.53 and -2.00 . Each oval represents a guide cannula tip at its most central point for each animal. Open ovals represent animals receiving saline and filled ovals represent the animals receiving raclopride, with the gray representing the lower dose ($0.25 \mu\text{g}$) and the black representing the higher dose ($0.75 \mu\text{g}$). Dotted ovals represent the placement for animals with unilaterally acceptable placements.

Postsurgery training. Rats were retrained daily on the baseline 500-ms task after cannula placement surgery until they met the criterion of 80% correct performance twice within 3 consecutive days of training. To determine whether there were any preexisting differences between the groups prior to drug infusions, two measures were examined: (a) the average percent correct trials on the days the rats met criterion, and (b) the number of days necessary to meet criterion. One-way ANOVAs were conducted for each variable, with drug group assignment as the between subjects factor. There were no differences in average percent correct trials, $F(2, 16) = 0.332$, $p = .722$, and in number of training days needed to meet criterion, $F(2, 16) = 2.32$, $p = .13$.

Infusion tests.

Accuracy. Performance on the infusion tests was first measured by accuracy (i.e., percentage of trials with correct response). The results (Figure 4A) suggest that the D2 antagonist raclopride did not influence accuracy, as seen by no effects of drug, $F(2, 16) = 1.643$, $p = .224$, testing, $F(3, 48) = 1.302$, $p = .29$, or their interaction, $F(6, 48) = 0.52$, $p = .79$.

Correct response latency. Performance in each of the infusion day tests was also assessed using response latency to nose poke the correct port. There was only a main effect of testing, $F(3, 48) = 3.244$, $p = .03$, with no main effect of drug, $F(2, 16) = 1.311$, $p =$

$.28$, and no interaction of drug and testing, $F(6, 48) = 0.559$, $p = .76$ (Figure 4B). Upon conducting six paired samples t tests comparing performance at the different infusion tests with a Bonferroni-adjusted significance level of $p = .008$, no significant differences emerged (all p s > 0.02). Although there were no significant differences across t tests, it is likely that the original main effect of testing is related to overall slightly longer latencies in the three challenge versions of the task compared with the 500-ms baseline task.

Omissions. The overall omission rates were low across all the testing sessions and did not differ among the drug groups (Figure 4C): testing, $F(3, 48) = 0.972$, $p = .414$, drug, $F(2, 16) = 0.802$, $p = .466$, and interaction, $F(6, 48) = 0.519$, $p = .791$.

Premature responses. Raclopride also did not influence the nose pokes to the ports made during the ready period (Figure 4D). There was only a significant main effect of testing, $F(3, 48) = 24.018$, $p < .001$, but not drug, $F(2, 16) = 0.417$, $p = .67$, or an interaction, $F(6, 48) = 0.985$, $p = .446$. Post hoc paired samples t tests were conducted with a Bonferroni-adjusted significance level of $p = .008$, and revealed greater levels of premature responses made in the variable ready period test compared with all other tests: 500 ms, $t(18) = -5.164$, $p < .001$; 100 ms, $t(18) = -6.174$, $p < 0.001$; and blink, $t(18) = 9.279$, $p < .001$.

Locomotor activity. Regardless of test or drug assignment, activity levels were comparable across all rats (see Table 4). There were no effects of drug, $F(2, 16) = 0.751$, $p = .488$, testing, $F(3, 48) = 1.684$, $p = .183$, or the interaction of these two variables, $F(6, 48) = 0.57$, $p = .752$.

Discussion

In this study, we have demonstrated that CeA D1, but not D2, receptors are important for maintaining adequate performance in this five-choice task. When D1 receptors in the CeA were temporarily inactivated using SCH 23390, response accuracy decreased when the ready period became variable from trial to trial or when the houselight blinked during the ready period. Furthermore, D1 receptor antagonism in the CeA resulted in more omissions and fewer premature responses in all three attentional challenges, as well as increased correct response latency when the houselight blinked during the ready period. This impairment in performance was significant in the group that received a higher dose of D1 antagonist SCH 23390, although this group showed better performance during the baseline training prior to the infusion. Thus, the preexisting differences were not likely to confound the subsequent results showing impairing effects of SCH 23390. Therefore, taken together, these data suggest that CeA D1 receptors play an important role in modulating performance during the five-choice task.

The increased omission rates observed in the current study fall within the range of what others have seen in cases when accuracy has been impaired as well as when accuracy has been relatively unaltered (e.g., Baunez & Robbins, 1999; Passetti, Dalley, & Robbins, 2003). Increased omission is generally interpreted as reflecting impaired attention when other measures, such as food cup latency, are not affected (as was the case in our study). However, it can also reflect nonattentional aspects, such as “response vigor,” described by Robbins (2002), as reflected by response latencies and rates of omissions. In

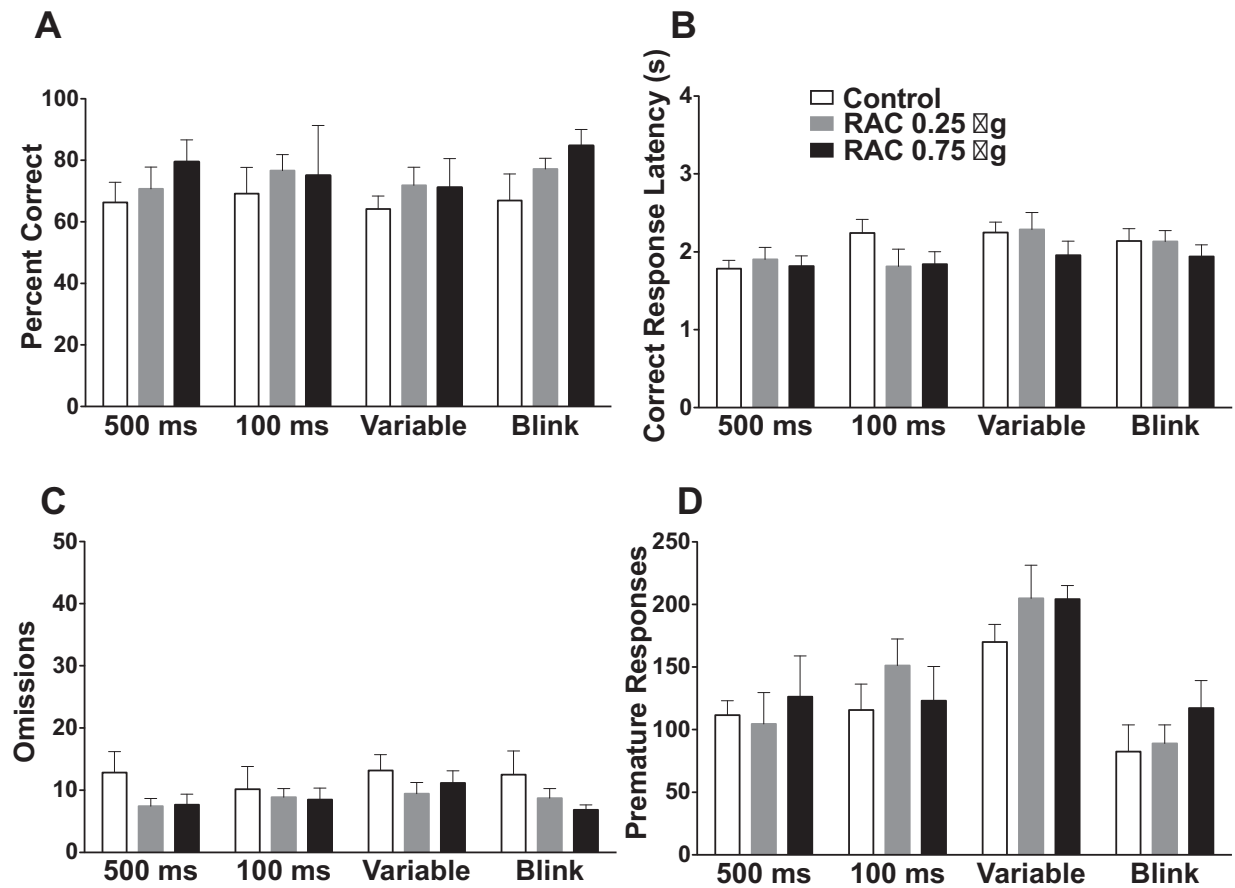


Figure 4. (A) Mean ($\pm$ SEM) percent trials with correct responses across all tests. (B) Mean ($\pm$ SEM) latency to make the first correct response. (C) Mean ($\pm$ SEM) numbers of trials with omissions (no nose pokes during the response time) across all tests. (D) Mean ($\pm$ SEM) numbers of premature responses (nose pokes to any ports during the ready period) across all tests. No significant differences were detected.

addition, a premature response in our study is likely to reflect the overall response vigor more than impulsive behavior, because in this procedure, premature responses do not result in any consequences (i.e., termination of the trial). Generally, in other versions of this task, the rat must withhold responding during the ready period in order to avoid a “time-out” period; therefore, premature responses are used to gauge inhibitory control over impulsivity (Robbins, 2002). However, in our version of the task, responses made during the ready period were not followed by time-out, and therefore premature responses are not necessarily related to a failure to inhibit responding and cannot be interpreted strictly as a measure of impulsivity. And as a consequence of this modification, the

number of premature responses tends to be higher in our procedure but comparable with other data sets using this same protocol (Olshavsky et al., 2014). Compared with the typical procedure of 5CSRTT, our procedure indeed exerts less stimulus control, and it is possible that our finding might be different if we used a task with more cue control. However, our results do not indicate such poor stimulus control that the rats failed to understand the stimulus–response contingencies. For example, a chance level performance would be responses to the lit port for 20% trials and 80% for the unlit ports. Our data show a range of 47 to 85% trial response to the lit port and 30 to 50% range to unlit ports, which suggests that the subjects sufficiently learned the contingency of the cue.

Table 4
Locomotor Activity Level in Experiment 2 (D2 Receptor Antagonism)

Group	500 ms	100 ms	Variable	Blink
Saline	470 $\pm$ 67.32	637.5 $\pm$ 70.58	581 $\pm$ 97.12	559.67 $\pm$ 64.28
Raclopride 0.25 μ g	533.43 $\pm$ 62.28	578 $\pm$ 86.64	570 $\pm$ 93.03	552.57 $\pm$ 88.04
Raclopride 0.75 μ g	617.67 $\pm$ 64.53	652.83 $\pm$ 80.42	666 $\pm$ 88.33	716.5 $\pm$ 78.08

Here we have demonstrated that D1, but not D2, receptors are necessary for successful performance in this five-choice task, which aligns with previous research investigating the roles of DA receptors in attention. Although systemic inactivation of DA receptors can result not in deficits in accuracy but in response vigor (Harrison, Everitt, & Robbins, 1997; Weed & Gold, 1998), local inactivation reveals a more nuanced story. For example, D1 receptors within the mPFC and striatum are necessary for task accuracy, whereas D2 receptor roles differ depending on the area under examination. In the mPFC, D2 receptor inactivation has little-to-no impact on performance in the 5-CSRTT (Granon et al., 2000), whereas striatal D2 receptors impact response latency (Agnoli, Mainolfi, Invernizzi, & Carli, 2013). Within the nucleus accumbens, D1 receptors appear to be important for performance during the 5-CSRTT (Pezze, Dalley, & Robbins, 2007): D1 receptor partial agonist SKF 38393 improved the accuracy and reduced omissions, whereas D1 receptor antagonist SCH 23390 decreased accuracy, and increased both omissions and correct response latencies. In contrast, D2 receptors in the nucleus accumbens do not seem to directly modulate attentional function, but instead influence the general performance including perseverative responses and food cup latency. Taken with existing work, our findings demonstrate the importance of D1 receptors in attentional performance and a more ambiguous role of D2 receptors.

Reduced performance by D1 receptor blockade in the CeA is not likely related to motor impairment or a simple inability or lack of motivation to perform the basic task. The activity levels examined during the sessions were comparable across all three groups. The Coulbourn activity monitor used in the current study is commonly used to measure activity levels in the conditioning chamber. For example, freezing behaviors are recorded using the same kind of monitors (Lee, Choi, Brown, & Kim, 2001; Lee & Kim, 1998). We have also detected enhanced activity levels in the same setup. In our unpublished work, systemic injection of D1 agonist SKF 829580 (0.25 mg/kg) significantly increased activity levels (831 beam breaks) compared with activity levels after saline injection (514 beam breaks) during a classical appetitive conditioning. Therefore, we believe our activity monitoring system is sensitive enough to record potential differences in activity levels. Furthermore, although the allotted response time was 5 s, the overall response latency was under 2 s, and specifically in rats with impaired performance, the response latency ranged from 2 to 3 s, demonstrating that the rats had enough time to complete the task. The range of the response latency seen in the current study is very similar to the ones reported by Holland et al. (2000), who initially used the modified version of the five-choice task. Their reported response latency was generally just below 2 s for control and CeA-lesioned groups, and was within 2 to 4 s for the CeA-lesioned group when performance was impaired. In addition, the rats infused with D1 antagonist in the current study were not any slower in collecting the food pellet once it was dispensed into the food cup. This suggests that the overall motivational levels were similar in terms of their willingness to retrieve the food reward. Although an effect of multiple infusions cannot be completely ruled out, given that each rat received a total of four infusions of the same drug and dose, this experiment was designed to minimize any possible multiple infusion effects. First, we used two different orders of the attentional challenges as shown in Table 2 and confirmed that order of attentional challenge tests did not result in

differences in performance levels. Furthermore, in addition to having two testing orders, we spaced infusions 48 hr apart with the intent of minimizing any potential effect of repeated infusions.

It has been previously demonstrated that D1 and D2 receptors are important for learning processes. Rats with systemic injections of D1 and D2 antagonists during a Pavlovian learning paradigm showed respective impairment and enhancement of conditioned food-cup approach when tested 24 hr later drug-free (Eyny & Horvitz, 2003). However, other work has shown that within the CeA, D1 and D2 receptors operate similarly to affect fear conditioning and conditioned place preference (CPP). Intra-amygdala (mostly targeting CeA) infusions of 2 μ g of SCH 23390 (D1 antagonist) and 1 μ g of eticlopride (D2 antagonist) prior to fear conditioning and/or prior to a retention test 24-hr postconditioning resulted in reduced freezing at the retention test (Guarraci et al., 1999, 2000). Similarly, intra-CeA infusions of 1.0 μ g of SCH 23390 or 0.5 μ g of Sulpiride (D2 antagonist) resulted in decreased acquisition of morphine-induced CPP (Rezayof et al., 2002; Zarindast et al., 2003). Instead of having opposing roles on Pavlovian appetitive learning, as is the case at the systemic level, D1 and D2 receptors within the CeA have similar roles in modulating fear and reward learning. Comparatively, we find that a 1.0- μ g dose of SCH 23390 in the CeA causes a decrement in attentional function, whereas neither dose (0.25 or 0.75 μ g) of the D2 antagonist raclopride had an impact on attentional functioning as measured by the five-choice task. The findings of our current study also align with our recent work examining CeA D1 and D2 receptor functions in another behavioral process called *disengagement behavior* (Smith et al., 2013). Disengagement behavior refers to the ability to stop or disengage from an ongoing behavior (i.e., drinking) to attend to an incoming stimulus such as perioral stimulation (Schallert & Hall, 1988). Depletion of dopaminergic input in the CeA caused a disruption in disengagement but not simple spontaneous orienting to perioral stimulation in the absence of ongoing activity, suggesting that CeA dopamine function is important for an attentional component of this behavior without affecting sensory information processing (Smith et al., 2013). In addition, using the same doses and antagonists used in the current study, we demonstrated that CeA D1 receptor antagonism impaired disengagement behavior, whereas D2 antagonism within the CeA had little to no impact on disengagement behavior. Although it cannot be completely ruled out that higher doses of D2 antagonist raclopride might influence the performance during the five-choice task, it seems unlikely because in a study that examined the role of CeA D2 receptors in fear and anxiety, intra-CeA infusions of 0.75 μ g raclopride (the same dose used in the current study) yielded the same results as higher doses (Pérez de la Mora et al., 2012). For example, intra-CeA infusions of either 0.75 or 2 μ g of raclopride increased the latency for the rats to bury an electrified probe, whereas the same two doses and a higher dose (4 μ g) had no effect on the rats' behavior on elevated plus maze. Thus, the maximal effect of raclopride in the CeA D2 receptors seems to have been achieved with 0.75 μ g.

The midbrain dopamine inputs to the CeA arise from both the Substantia nigra compacta (SNc) and the ventral tegmental area (VTA; Oades & Halliday, 1987; L. W. Swanson, 1982). However, our previous study suggests that the nigral dopamine input might be more important for modulating CeA's function. Injection of 6-hydroxydopamine into the CeA, which caused disengagement

deficits, resulted in a decrease in dopaminergic cells in the SNc but not in the VTA, suggesting that dopaminergic input from the SNc is important for successful disengagement behavior (Smith et al., 2013). We have also shown that intact nigral dopamine and CeA connections are crucial in processing enhanced attention driven by prediction error (Lee et al., 2006, 2008). Furthermore, blocking the communication between the VTA and the CeA does not result in the same deficits in enhanced orienting to a visual conditioned stimulus as when the SNc–CeA communication is blocked (Lee et al., 2011, 2005). Others have also shown that MPTP injections that caused significant reduction in the nigrostriatal dopamine fibers in mice also resulted in significant reduction of dopamine fibers in the CeA (von Bohlen und Halbach, Schober, Hertel, & Unsicker, 2005). Although the VTA's input to the CeA cannot be ruled out, it is most likely that it is the SNc dopaminergic input into the CeA plays an important role in attentional processing.

Among the many neural circuits that are involved in regulating attention, the CeA might modulate attention through the basal forebrain cholinergic system, known to play a crucial role in attentional function (Harati, Barbelivien, Cosquer, Majchrzak, & Cassel, 2008; McGaughy, Dalley, Morrison, Everitt, & Robbins, 2002; Risbrough, Bontempi, & Menzaghi, 2002). The CeA can influence the basal forebrain cholinergic system via its direct projections to the SI/nBM (Fritz, Yilmazer-Hanke, Roskoden, Schwegler, & Linke, 2005), which, as a part of the basal forebrain system, in turn sends cholinergic projections to cortex, including the PFC (Mesulam, Mufson, Wainer, & Levey, 1983). The SI/nBM and its projections to the PFC are integral for visual attention during the 5CSRTT (McGaughy et al., 2002). Furthermore, it has been shown that the connections between the CeA and SI/nBM are also necessary for maintaining accuracy in a similar task (Holland, 2007), and that the elimination of cholinergic inputs to the PFC, as well as lesions of the CeA, produce similar deficits in the multiple-choice reaction task (Maddux et al., 2007). Similarly, cholinergic cells in the SI/nBM and their projections to the posterior parietal cortex, as well as the CeA, play an important role for enhanced attentional processing driven by prediction error (Bucci, Holland & Gallagher, 1998; Chiba, Bucci, Holland & Gallagher, 1995; Maddux et al., 2007)—the same attentional processing modulated by the SNc–CeA connections (Lee et al., 2006, 2008). Therefore, the CeA might modulate attentional function via its connections to the cortical cholinergic system.

However, the role of CeA's substantial reciprocal connections to the SNc cannot be ruled out (Fudge & Haber, 2000; Gonzales & Chesselet, 1990). It is possible that the CeA could be modulating attentional function through the nigrostriatal dopaminergic system, which, in concert with the PFC, is also crucial for maintaining adequate performance in the 5-CSRTT (Rogers, Baunez, Everitt, & Robbins, 2001; Christakou, Robbins, & Everitt, 2001). Nigrostriatal dopamine depletion (Baunez & Robbins, 1999), but not necessarily ventral striatal dopamine depletion (Cole & Robbins, 1989), impairs accuracy when the presentation of the portlight becomes unpredictable. In the current study, the higher dose of D1 antagonist SCH 23390 also significantly impaired accuracy when the ready period varied. Reducing temporal predictability of the visual targets is likely to require higher levels of readiness or alertness to respond. Therefore, CeA D1 receptors might be important for modulating this aspect of attentional processing. In addition to the modulation of attentional function, the CeA's

connections to the nigrostriatal pathway can also influence other factors influencing performance during the five-choice task. Bilateral lesions of the medial portion of the striatum significantly affected all aspects of performance during 5CSRTT, including response vigor (Rogers et al., 2001). In the same study, lateral striatal lesions resulted in severe performance deficits (i.e., increased omission) that precluded them from completing the task. More specific nigrostriatal dopamine depletion also increased omission and correct response latency, with a minor impact on accuracy (Baunez & Robbins, 1999). Therefore, the CeA might also play a role in modulating response vigor via its connections to the nigrostriatal pathway.

The current experimental preparation used to study the roles of CeA dopamine receptors in attention may give insight into diseases that are characterized by aberrant dopaminergic function. Specifically, Parkinson's disease (PD)—primarily known as a motor disorder because of the hallmark nigrostriatal dopamine loss—also features attentional dysfunction, even in the early stages of disease (Filoteo et al., 1997; Swanson et al., 2000; Woodward, Bub, & Hunter, 2002; Yamaguchi & Kobayashi, 1998; Zhou et al., 2012). Dysfunction of the mesocortical system is suggested to be responsible for PD-related cognitive problems; however, cortical areas typically are among the last regions to show pathological changes in PD (Alafuzoff et al., 2009; Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici, 2004), and drug therapy targeted to restore prefrontal function is not consistently effective at improving attentional deficits in PD patients (Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Owen et al., 1993). Thus, extracortical regions are likely to contribute to attentional deficits, especially in the early stages of disease. Therefore, the loss of SNc dopaminergic input into the CeA might contribute to the attentional dysfunctions associated with PD. This work also has implications for other disorders beyond PD. Dysfunction of the dopamine system is often seen in disorders accompanied by attentional issues, such as attention-deficit hyperactivity disorder, depression, and schizophrenia (Abi-Dargham, 2004; Aleman & Kahn, 2005; Braak et al., 1994; di Michele, Prichep, John, & Chabot, 2005; Fudge & Emiliano, 2003; Laurens, Kiehl, Ngan, & Liddle, 2005; J. M. Swanson et al., 2000). Thus, examining dopamine functions in the CeA will broaden our understanding of the neural mechanisms responsible for attentional deficits associated with PD and various other mental disorders.

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