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Regional differences in dopamine receptor blockade affect timing impulsivity that is altered by d-amphetamine on differential reinforcement of low-rate responding (DRL) behavior in rats

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ABSTRACT

The ability to control when to start an action and when to stop is crucial in human and animal behavior. A failure to suppress premature behavior or to carry out an action in a timely manner is commonly seen in several neuropsychological disorders. Despite the phenomenon, the exact neural mechanisms underlying this timing impulsivity remain to be elucidated. Systemic injection of D-amphetamine (AMP) has been shown to disrupt rat's performance in the differential reinforcement of low-rate (DRL) task that requires both optimal timing and proper impulsive control as measured by peak time and non-reinforced responses, respectively. By directly infusing selective D1 or D2 receptor antagonists (SCH23390 and raclopride, respectively) into three brain areas, we aimed to uncover which brain regions and which dopamine receptor subtypes are involved in counteracting the rat's deficit of DRL performance induced by the systemic injection of AMP. We found that D1, but not D2 receptors in the dorsal hippocampus (dHIP) and nucleus accumbens (NAC) played an important role in impulsive control as well as in timing. In the medial prefrontal cortex (mPFC), both D1 and D2 receptors played an equal role in impulsive control, but only mPFC D1 was critical in the control of timing. Together, our data revealed a regional-dependent and dopamine receptor subtype specific effect across each region tested in the mesocorticolimbic circuits on the deleterious effect of AMP in the DRL task. The current findings further advance our understanding of the neurobehavioral mechanisms involved in timing impulsivity.

1. Introduction

The ability to control when to start an action and when to stop is crucial in human and animal behavior. A failure to suppress premature behavior or to carry out an action in a timely manner is a common behavioral phenotype; such lack of impulsive-control and/or failure to inhibit urge, in contrast to functional impulsivity, can be seen in neuropsychiatric disorders such as attentional deficit hyperactivity disorder (ADHD), drug addiction, and pathological gambling or shopping. Impulse-control, as a multifaceted construct, can be separated into impulsive action and impulsive choice. In the domain of impulsive action, with respect to inhibitory dysfunction, "failing to wait" can be measured in experimental rodents using the 5-choice serial reaction time (5-CSRT) task and differential reinforcement of low-rate responding (DRL) schedule controlled behavior [1–4]. Research findings have mainly involved 5-CSRT when investigating the neurobiology and psychopharmacology of impulsive action. Surprisingly, little is known about DRL behavior used to address the neuropharmacology of impulsive action. It is noted that the behavioral performances characterized in these two tasks are discrepant. For example, the DRL behavior does not provide an external cue like the 5-CSRT does. In the 5-CSRT task, animals are trained to execute a correct choice behavior based on visually attending an external cue. In contrast, the DRL procedure does not provide such an external cue; rather, the subject relies on the internal representation of the passage of time since a prior response. Based on this external vs. internal difference, the DRL behavior is thought to be a more accurate measure of "wait" in time as compared to the 5-CSRT [1,2,4]. It is then important to examine the potentially distinct component of impulsive action involved in the DRL behavior.

Operant behavior maintained during the DRL schedule has been characterized as showing temporal regulation [5–10] as well as

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behavioral inhibition [11–15]. Rats trained in the DRL schedule are required to inhibit or withhold lever press for a minimum specified period of time (usually 5 s to 72 s) in order to obtain a reinforcer. An early/premature response before the criterion time will reset the program clock and then the subject has to wait again for the specific set of time, starting from the time the non-reinforced response was made. This reset or "penalty" distinguishes the DRL procedure from other schedules of reinforcement such as the fixed-ratio (FR) schedule and the fixed-interval (FI) schedule, both of which generate a relatively high rate of responding. In addition, the DRL task is also distinct from other temporal discrimination tasks, such as the discrete-trial temporal bisection task, and from temporal differentiation tasks, such as the peak procedure; this is because these tasks do not involve a program clock reset following a premature response [16–18]. In considering the timing process that has been proposed to be involved in the impulsive control [1,19], the DRL behavioral task is suitable for the study of timing impulsivity. It should also be noted that the exact neural basis underlying the timing and impulsive action of DRL behavior so far remains largely unknown.

Substantial evidence has shown that DRL behavioral responses are profoundly affected by the systemic administration of D-amphetamine (AMP) and other psychostimulants [20]. While a considerable number of studies have shown that the level of extrasynaptic dopamine (DA) in the brain is significantly increased by AMP [21], whether DA-dependent mechanisms underlie the AMP in affecting DRL behavior remains unclear. Based on previous findings that the mesocorticolimbic circuits are involved in behavioral inhibition or impulsive action [2,22,23], we hypothesized that behavioral inhibition and temporal processing involving DRL behavior may be mediated by various anatomical areas within the mesocorticolimbic DA systems, as well as by a variety of pharmacological substrates. Thus, this study investigated the possible brain region-specific and receptor-specific dopaminergic modulation of AMP-altered DRL behavior by directly infusing a selective D1 or D2 receptor antagonist (SCH23390 or raclopride, respectively) into three DA terminal areas of the brain in rats: the medial prefrontal cortex (mPFC), the nucleus accumbens (NAC), and the dorsal hippocampus (dHIP).

2. Materials and methods

2.1. Subjects

Sixty male Wistar rats, averaged approximately 250 g of body weight upon receipt, were purchased from the Breeding Center of Experimental Animals in National Taiwan University Hospital, Taipei, Taiwan. The rats were housed individually. After 10 days of adaptation with food and water provided ad libitum, the rats were maintained on a water-restriction regimen such that there was 5 min access to tap water in the home cage occurring no sooner than 30 min after the end of each daily experimental session. The rats were monitored and kept at 85% of their pre-restriction body weight during the entire experiment. Food pellets were continuously available in each home cage. All procedures were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by an institutional review committee.

2.2. Apparatus

The interior dimensions of each operant chamber were 20 × 25 × 30 cm (MED Associated, St. Albans, VT, USA). Aluminum panels formed the front and back walls, and clear Plexiglas comprised the remaining sides and the top. Stainless steel rods (with a diameter of 5 mm) were set 11 mm apart to provide flooring. Each chamber was equipped with a lever positioned 7.3 cm above the floor and 4 cm from the right corner of the front panel. A liquid dispenser was set outside of the front panel of the chamber. The reinforcer delivery mechanism gave 0.04 ml of tap water at each presentation. The water was delivered into a receiving dish (25 mm diameter) located at the center of the front panel and 2 cm above the floor. The chamber was illuminated by a small light bulb located 10 cm above the floor and positioned 5 cm from the left corner of the front panel. Each chamber was enclosed in a plywood box with a fan to provide necessary ventilation and to mask any outside noise. A set of four operant chambers was connected with a PC to control the operant variables and data collection via an in-house designed program [9,10,24].

2.3. Surgery

Under sodium pentobarbital (40 mg/kg; IP) anesthesia, each rat was placed in the stereotaxic instrument (David Kopf Instruments) for the bilateral implantation of stainless steel cannulae. As determined by Paxinos and Watson [25], the coordinates for the final injection sites were: AP = +3.7 mm, L = ± 0.7 mm, D = −4.5 mm for the mPFC; AP = +1.7 mm, L = ± 1.8 mm, D = −6.5 mm for the NAC and AP = −3.2 mm, L = ± 2.2 mm, D = −3.2 mm for the dHIP. Stainless steel stylets were inserted into the guide cannulae to keep the guides patent until the microinjections were conducted. At the end of surgery, penicillin (50000 I.U.) was administered intramuscularly to prevent infection. Subjects were allowed 7 days to recover from surgery.

2.4. Drugs and microinjection

D-amphetamine sulfate (Sigma Chemical Co.; St. Louis, MO, USA), SCH23390 HCl (Tocris Cookson; Bristol, UK), and raclopride L-tartrate (RBI; Natick, MA, USA) were dissolved in 0.9% physiological saline (SAL). The vehicle solution was 0.9% physiological saline. At the time of microinjection of SCH2330 (SCH) or raclopride (RAC), the stylets were replaced by 28 gauge injection needles connected by PE20 tubing to 2 μl Hamilton micro-syringes. Each drug or vehicle solution was locally infused in a volume of 0.25 μl over 1 min per site for a total duration of 2 min. The injector needles were extended from the bottom of the guide cannulae for 1.0 mm in the dHIP group and 1.5 mm in both the mPFC and NAC groups. After injection, the needles were left in place for an additional minute to enhance diffusion from the injection site and to reduce the possibility of reflux. To ensure an equal binding to the receptors, we chose to deliver the drugs in equal molecular weight (in nmol) for the D1 and D2 antagonists in the entire study.

2.5. Procedures

The rat received DRL–10 s behavior training with procedures described previously [24][e.g. 24]. In brief, after basic lever response training, the DRL–5 s task was introduced for fifteen daily sessions, followed by at least thirty daily sessions for DRL–10 s before the intracranial cannulation surgery was carried out. After post-surgery recovery, the rats received five additional daily sessions of retraining to ensure stable performance before drug tests. All daily training or test sessions lasted for 15 min.

Pharmacological testing was conducted to examine whether the performance regarding DRL–10 s behavior was changed by systemic AMP treatment and whether this could be reversed by local infusion of a selective DA receptor antagonist into the selected brain areas. There were three groups of rats, each prepared with the microinjection cannula aimed at the mPFC, NAC, or dHIP. Half of the rats in each group received SCH treatment while the other half received RAC treatment (n = 10 each). The systemic injection of AMP or saline vehicle was administered intraperitoneally (i.p.) 15 min before the behavioral session commenced and the intra-cranial microinjection of SCH, RAC or vehicle was infused right before the systemic injection. The dose of AMP, 1 mg/kg, was selected based on previous reports [9,20], specifically avoiding a too high dose that can bring down operant responses. In each test, a given rat received two drug injections, one being a systemic administration and one being a microinjection, on

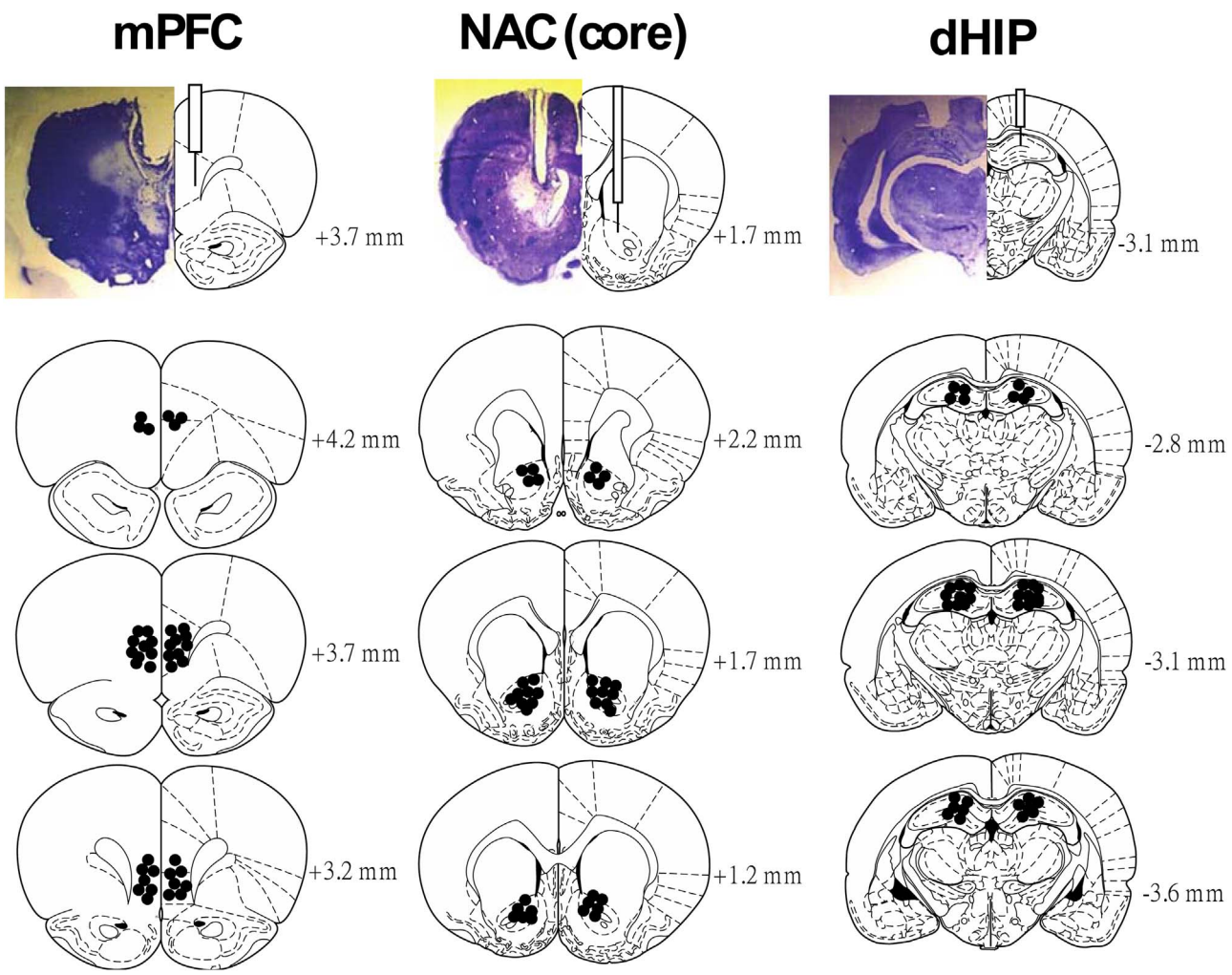

Fig. 1. Distribution of infusion needle tips in the medial prefrontal cortex (mPFC), the nucleus accumbens (NAC), and the dorsal hippocampus (dHIP) obtained from samples of the experimental subjects. The plates of coronal brain sections were adapted from [25].

each of the six pharmacological test days. The pharmacological tests were conducted in the following order (microinjection-systemic injection): SAL-SAL, SAL-AMP, low-dose-DA-antagonist −SAL, low-dose-DA-antagonist −AMP, high-dose-DA-antagonist −SAL, and high-dose-DA-antagonist-AMP. In the last four drug tests, the high and low doses of DA antagonist given alone or with AMP were counterbalanced across the subjects within the group; namely, half of the rats received low dose of antagonist first while the remaining rats received high dose of antagonist. Between each of these six drug treatments there were at least one daily session of baseline training (or washout sessions) in order to ensure no carryover of drug effects from the previous injections.

2.6. Histology

After completion of drug tests, rats were sacrificed via an overdose of sodium pentobarbital. Brains were removed and fixed in a sucrose/formalin mixture for at least 24 h. The brain was frozen and sliced in 40 μm sections. The mounted slices were stained with cresyl violet to verify the locations of drug infusion. Only rats that had bilateral needle tracks terminating in the mPFC, NAC or dHIP (Fig. 1) were included in the data analysis (the final *n* for each group shown in Table 1).

2.7. Data collection and statistics

Each lever press was classified in terms of its associated inter-response time (IRT; the time in millisecond elapsed since the prior response); and the resulting dataset on IRT was grouped and plotted into a distribution consisting of response frequencies for 21 consecutive 1 s time bins. For the quantitative analyses, there were six dependent variables including 1) total responses, 2) reinforced responses – lever press with IRT $>=10$ s, 3) non-reinforced responses – lever press with IRT <10 s, 4) burst responses – lever response with IRT <2 s, 5) peak rate and 6) peak time. The burst responses were the summed responses with IRTs that were less than 2 s (as shown in bins 1 and 2 of the IRT distribution curves in Figs. 2–4). The peak time and peak rate were calculated from the de-burst IRTs (IRT >2 s), in which a moving average based on four consecutive 1-s bins with a 1-s step size was applied to smooth the distribution. After the maximum frequencies for a 4-s epoch were identified, the peak time was the average value (in millisecond) of all the IRTs that fell within those four bins (i.e., the maximal epoch). The peak time measure indicates at which time point the rats pressed the lever with the highest IRT frequency, namely their expected time for obtaining the reinforcer. The peak rate was calculated from the summed responses in those four bins divided by four, indicating how strongly the rats were motivated to press the lever at the expected criterion time. This smoothing procedure has been utilized previously [9,10,24,26,27].

In order to evaluate the effects of local infusion of the selective DA receptor antagonist on AMP altered DRL behavior, each of the six dependent measures was separately subjected to one-way repeated measures ANOVA and followed by a Fisher LSD *post hoc* test if the

Table 1
The effects of SCH23390 and raclopride locally infused into three selected brain areas on d-amphetamine (AMP; 1 mg/kg, i.p.) induced behavioral changes in the DRL–10 s task on four quantitative measures.

	SCH23390 (SCH, n = 10) Low: 3 nmol; High: 30 nmol					Raclopride (RAC, n = 10) Low: 3 mol; High: 30 nmol				
	Total Response	Reinforced Response	Burst Response	Peak Rate	Missing data	Total Response	Reinforced Response	Burst Response	Peak Rate	Missing data
(A) Medial Prefrontal Cortex (mPFC)										
SAL-SAL	108.7 ± 10.7	40.7 ± 2.8	22.9 ± 10.6	12.5 ± 1.1	0	127.2 ± 7.47	34.3 ± 2.8	38.4 ± 7.3	15.2 ± 0.6	0
SAL-AMP	*150.1 ± 17.6	*17.6 ± 1.7	37.6 ± 11.1	*17.1 ± 2.0	0	*163.0 ± 14.1	*19.4 ± 2.3	*58.0 ± 12.	15.8 ± 0.8	0
Low-SAL	118.1 ± 11.3	37.9 ± 2.0	31.1 ± 10.0	12.7 ± 1.1	0	129.6 ± 8.41	36.3 ± 2.9	41.0 ± 8.7	15.0 ± 0.6	0
Low-AMP	135.2 ± 16.0	*22.0 ± 2.2	30.8 ± 8.10	14.7 ± 1.8	1	142.5 ± 12.9	*22.0 ± 2.5	41.3 ± 10.	15.1 ± 1.1	0
High-SAL	82.4 ± 6.1	*47.0 ± 3.7	4.8 ± 2.0	11.2 ± 1.1	5	109.4 ± 8.92	38.2 ± 2.6	26.0 ± 7.1	12.7 ± 1.1	0
High-AMP	*76.0 ± 14.0	*32.0 ± 5.1	0.0 ± 0.0	10.0 ± 2.8	5	124.2 ± 16.1	29.4 ± 1.9	32.7 ± 13.	12.3 ± 1.0	0
	SCH23390 (SCH, n = 10) Low: 3 nmol; High: 30 nmol					Raclopride (RAC, n = 10) Low: 3 mol; High: 30 nmol				
	Total Response	Reinforced Response	Burst Response	Peak Rate	Missing data	Total Response	Reinforced Response	Burst Response	Peak Rate	Missing data
(B) Nucleus Accumbens (NAC)										
SAL-SAL	131.0 ± 8.3	32.4 ± 2.18	30.4 ± 7.9	13.8 ± 0.8	2	118.1 ± 7.09	34.6 ± 3.36	18.9 ± 5.5	14.2 ± 0.7	0
SAL-AMP	145.8 ± 11.	*17.9 ± 2.16	31.0 ± 8.3	16.5 ± 1.3	0	*177.4 ± 23.8	*15.5 ± 2.89	*43.9 ± 16.	*22.1 ± 3.7	1
Low-SAL	106.5 ± 10.	39.4 ± 3.00	19.8 ± 7.5	10.4 ± 0.8	0	90.1 ± 8.3	41.4 ± 2.21	9.29 ± 4.4	9.93 ± 0.9	2
Low-AMP	108.3 ± 11.	30.3 ± 4.53	22.1 ± 7.4	11.0 ± 2.5	1	152.0 ± 14.5	*21.9 ± 2.98	27.3 ± 9.4	19.3 ± 3.1	2
High-SAL	*73.3 ± 11.	36.0 ± 3.46	*5.57 ± 1.8	*8.79 ± 1.5	3	113.7 ± 7.04	33.7 ± 2.79	16.4 ± 4.4	12.2 ± 0.5	2
High-AMP	*86.9 ± 12.	33.1 ± 2.89	*8.13 ± 2.7	*8.69 ± 1.5	2	*165.0 ± 15.7	*13.6 ± 1.86	33.0 ± 9.0	*22.4 ± 2.5	1
	SCH23390 (SCH, n = 10) Low: 3 nmol; High: 30 nmol					Raclopride (RAC, n = 10) Low: 3 mol; High: 30 nmol				
	Total Response	Reinforced Response	Burst Response	Peak Rate	Missing data	Total Response	Reinforced Response	Burst Response	Peak Rate	Missing data
(C) Dorsal Hippocampus (dHIP)										
SAL-SAL	109.9 ± 4.3	38.6 ± 2.26	19.8 ± 3.5	15.1 ± 0.5	0	107.8 ± 3.6	38.7 ± 0.9	19.0 ± 2.8	12.2 ± 0.9	0
SAL-AMP	124.0 ± 6.9	*22.1 ± 2.20	19.1 ± 5.0	17.9 ± 1.1	0	123.8 ± 12.8	*22.2 ± 1.8	22.1 ± 7.9	*14.9 ± 1.6	1
Low-SAL	96.0 ± 10.	38.2 ± 4.30	11.0 ± 3.2	14.5 ± 1.5	0	105.1 ± 3.5	39.1 ± 2.9	14.2 ± 3.9	12.9 ± 1.0	0
Low-AMP	109.4 ± 9.1	*27.0 ± 2.76	9.89 ± 3.6	15.1 ± 1.3	0	*131.0 ± 12.	*23.7 ± 2.8	23.5 ± 10.	*15.0 ± 1.4	0
High-SAL	*59.0 ± 7.7	41.3 ± 4.59	*2.3 ± 1.2	*7.61 ± 1.5	2	97.9 ± 7.7	39.8 ± 1.5	10.1 ± 3.3	11.4 ± 1.0	0
High-AMP	*81.3 ± 3.7	40.0 ± 2.64	*4.7 ± 1.1	*11.5 ± 0.9	0	121.5 ± 4.8	*24.1 ± 2.2	15.8 ± 4.7	*15.8 ± 1.0	0

Note: Four quantitative measures of the DRL–10 s performance – Total Response, Reinforced Response, Burst Response and Peak Rate are listed here together with the number of subjects in missing data for each drug test. (A) data from the groups with SCH23390 (left columns) and raclopride (right columns) infused into the mPFC; (B) data from those for the NAC; and (C) data from those for the dHIP. The other two quantitative measures – Non-Reinforced Response and Peak Time were scrutinized in the Results Section as well as plotted in Figs. 2–4 and thus these data are not listed in this table. They are listed in Table 3.The data points with significant Fisher LSD *post-hoc* test results in comparison with the SAL–SAL condition are denoted with a "*". Data are represented as Mean ± S.E.M.

ANOVA test was significant [28]. There were several cases of missing data (see Table 1) due to a high level of balking or akinesia by drug, defined by a rat emitting fifteen responses or less within a session. For each case, the missing data were replaced by the group mean calculated from the values obtained from the remaining subjects in the same group receiving the same drug treatment (mean imputation) [29,30]. To solve a possible tendency of underestimating group variance by the method of mean imputation, we also conducted stochastic regression imputation in the groups that have more than 10% of missing data rate. The stochastic regression imputation was conducted using the open-source R software with the package "mice" [31,32]. To test regional differences in dopamine receptor blockade involved in timing impulsivity in AMP altered DRL behavior, a three-way ANOVA (between factors – brain regions and receptor subtype antagonists and within factor – drug treatments) was additionally conducted for either non-reinforced responses or peak time. The significance level was set at $p < 0.05$ for all tests. The data are all presented as means ± S.E.M.

3. Results

3.1. Effects of systemic injection of AMP on DRL behavior

Following the training and post-operation training, when under the SAL–SAL condition, all ten groups of rats performed the DRL–10 s behavior in a steady state with their IRT distribution consistently showing a peak located close to the 10 s criterion time (see the white-circle-dashed functions in Fig. 2–4). Consistent with our previous reports [9,26], the injection of 1 mg/kg AMP significantly affected DRL–10 s behavior by increasing the total, non-reinforced, and burst responses while decreasing the reinforced responses. Furthermore, AMP appeared to shift the peak of the de-burst responses horizontally to the left in the IRT distribution as consistently observed in all six groups of rats when tested under different experiments (see the black circle lines in Fig. 2–Fig. 4), which was verified by the significant decrease of peak time. The analyses of the IRT data for AMP treatment compared to the saline control (SAL-SAL) are shown in panels B, C, E, and F on each of Figs. 2–4 as well as in the corresponding columns in Table 1. We further examined whether there was any systematic change between non-reinforced responses and peak time. Correlation analysis showed that among the six groups of rats, none of the correlation coefficients reached significant levels (all $p > 0.05$) under the SAL–AMP condition. Under SAL-AMP, only three groups showed significant correlations. Thus, we concluded that the two dependent measures did not show systematic correlations in our data, further suggesting that the idea of impulsivity and timing are dissociable.

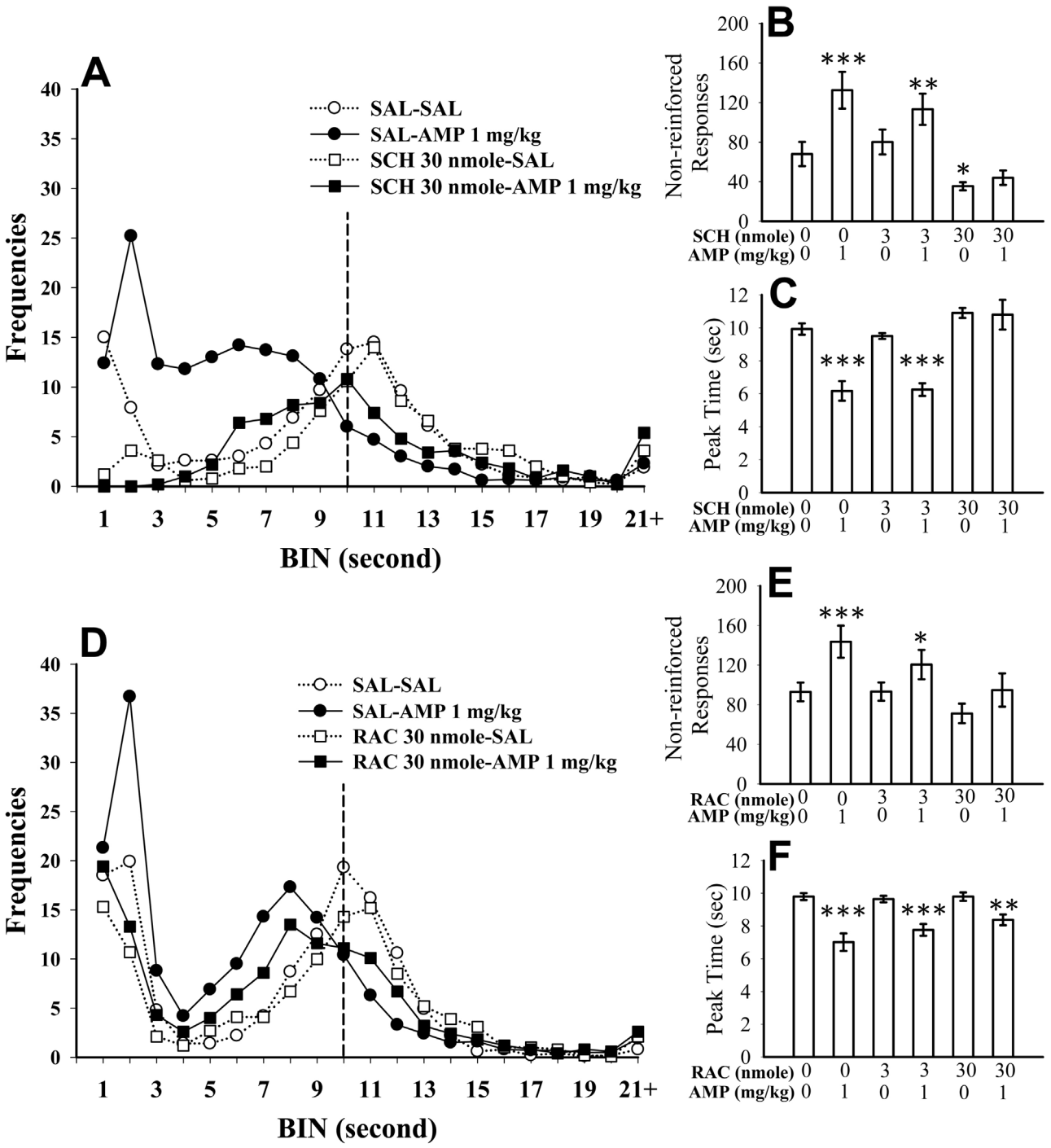

Fig. 2. The effects of SCH23390 (SCH, A–C) and raclopride (RAC, D–F) locally infused in the medial prefrontal cortex (mPFC) on d-amphetamine (AMP) induced behavioral changes in the DRL–10 s task. The rats received two drug administrations in each of six treatments with a sequential order of saline microinjection and saline (i.p.) injection, saline microinjection and AMP (i.p.) injection, microinjection of dopamine receptor antagonist (given at low or high dose as shown) with a saline (i.p.) injection, and a microinjection treatment of dopamine receptor antagonist combined with AMP (i.p.) injection. (A) and (D): IRT distributions from two groups of rats respectively tested for SCH (A) and RAC (D) under treatments with the saline control (SAL-SAL; open circles), the AMP treatment (SAL-AMP; filled circles), the dopamine receptor antagonist treatment (SCH-SAL or RAC-SAL; open squares) and the combined treatment of dopamine receptor antagonist and AMP (SCH-AMP or RAC-AMP; filled squares). Notice that two IRT distribution curves regarding the treatment with a lower dose of dopamine receptor antagonist with saline and its combination with AMP are not included in (A) or (D) for clarity of figure. (B) and (E): Non-reinforced responses of DRL behavior under the treatments are denoted. (C) and (F): Peak times derived from IRT data under the treatments are denoted. Asterisks denote significant differences in the Fisher LSD *post hoc* comparisons between the indicated drug treatment and the SAL–SAL condition. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

3.2. Effects of intra-mPFC SCH and RAC on AMP altered DRL behavior

Regarding to non-reinforced responses, one-way ANOVA yielded significant treatment effects in Fig. 2B ($F_{(5,45)} = 12.5$, $p < 0.001$) and in Fig. 2E ($F_{(5,45)} = 7.3$, $p < 0.001$). *Post hoc* comparisons revealed differences between the SAL-AMP and SAL–SAL conditions in Fig. 2B ($p < 0.001$) and in Fig. 2E ($p < 0.001$). These findings confirmed the increase of non-reinforced responses by AMP alone. When DA antagonists were microinjected in the mPFC, low dose (3 nmol) of both SCH and RAC failed to counteract AMP's effect, but high dose of both drugs successfully reduced AMP's effect on the non-reinforced responses. In addition, microinjection of SCH, but not RAC, at the high dose by itself

reduced the non-reinforced responses.

In the measure of peak time, the drug treatment effects were significant as confirmed by ANOVA in Fig. 2C ($F_{(5,45)} = 16.8$, $p < 0.001$) and Fig. 2F ($F_{(5,45)} = 16.5$, $p < 0.001$). *Post hoc* comparisons indicated that the systemic injection of AMP alone consistently and reliably decreased the peak time as shown in the 2nd bar from the left of Fig. 2C and a similar result was obtained in Fig. 2F. Although the low dose of both DA antagonists failed to counteract AMP injection, the high dose of SCH successfully reversed the peak time that was deceased by AMP, resulting in the peak time not different from the control condition. Thus, when a high dose of 30 nmol antagonist was infused into the mPFC, D1, but not D2, antagonist was able to attenuate the AMP-decreased peak time.

The other four quantitative measures of the DRL behavior, namely total responses, reinforced responses, burst responses and peak rate, are listed in Table 1A which also includes the number of subjects with missing data. Five rats in the intra-mPFC SCH experimental group failed to make minimal responding when the high dose of SCH was infused. This justified that the high dose of DA antagonist was lowered from 30 to 10 nmol in subsequent experiments.

3.3. Effects of intra-NAC SCH and RAC on AMP altered DRL behavior

In Fig. 3, on measuring the non-reinforced responses, the drug treatment effects were significant in Fig. 3B ($F_{(5,45)} = 11$, $p < 0.001$) and Fig. 3E ($F_{(5,45)} = 15.2$, $p < 0.001$). As compared to the control, *Post hoc* comparisons in Fig. 3B revealed differences in the SAL-AMP, SCH-SAL (both 3 and 10 nmol), and high-dose-SCH-AMP. This indicates that AMP alone significantly increased non-reinforced responses; while SCH in both doses alone reduced non-reinforced response to below control levels, and so was the high dose of SCH in combination with AMP. A different pattern was seen in the RAC-treated group (Fig. 3E) in that only the low dose of RAC by itself reduced non-reinforced responses; and, both doses of RAC failed to reverse systemic AMP's effect. That is, whenever AMP was administered, the non-reinforced responses were increased, even in the presence of RAC in the NAC. It is worth noting that the reduction of non-reinforced responses by either SCH or RAC in the NAC was not due to general motor deficits, which would have simply made the rats respond much less or no response at all. Instead, the reinforced responses in all cases of SCH or RAC treatment remained comparable to (or slightly higher than) the one under the SAL–SAL condition as shown in Table 1B. Thus, the reduction effect of SCH and RAC in the NAC was truly on impulsivity rather than on general motor deficits.

In regard to peak time, one-way ANOVA showed significant differences in Fig. 3C ($F_{(5,45)} = 8.3$, $p < 0.001$) and Fig. 3F ($F_{(5,45)} = 19.5$, $p < 0.001$). *Post hoc* comparisons indicated that AMP significantly decreased the peak time. In drug combination treatments, both doses of SCH successfully reversed AMP's effect on peak time while RAC failed to reverse such an effect. The results for the other four measures for these two groups are shown in Table 1B.

3.4. Effects of intra-dHIP SCH and RAC on AMP altered DRL behavior

For the non-reinforced responses, one-way ANOVA confirmed drug effects in Fig. 4B ($F_{(5,40)} = 20.8$, $p < 0.001$) and in Fig. 4E ($F_{(5,40)} = 7.0$, $p < 0.001$). *Post hoc* comparisons revealed differences between SAL–SAL and the following conditions in Fig. 4B: SAL-AMP, 10 nmol SCH-SAL, and 10 nmol SCH-AMP. These results indicate that AMP injection alone significantly increased non-reinforced responses while the high dose of SCH in the dHIP alone decreased it. When co-administered, the AMP-increased non-reinforced responses were significantly reversed by the 10 nmol SCH. It is worth noting that the decrease of non-reinforced responses by 10 nmol SCH was not due to general motor deficits because the number of reinforced responses was not affected (Table 1C). In contrast, infusion of RAC at both low and high doses in the dHIP had no effects either by itself or when co-administered with AMP.

For the measure of peak time, one-way ANOVA showed significant differences in Fig. 4C ($F_{(5,40)} = 15.4$, $p < 0.001$) and Fig. 4F ($F_{(5,40)} = 18.0$, $p < 0.001$). *Post hoc* comparisons confirmed that AMP significantly decreased peak time when this drug was given in combination with SAL infused into the dHIP as compared to the control. Both SCH and RAC at low dose failed to reverse the reduction in peak time induced by AMP as compared to the control. When given at high dose, RAC still failed to reverse the effects of AMP; conversely, SCH was able to reverse the decrease of peak time induced by AMP. In contrast to systemic AMP, the intra-dHIP SCH given at the high dose by itself significantly increased the peak time, resulting in a right-ward shift of the IRT curve. The results for the other four measures for these two groups under drug treatments are shown in Table 1C.

3.5. Summary of pharmacological tests

To sum up the results across three brain regions microinjected with D1 and D2 receptor antagonists and with or without systemic AMP, we conducted a mixed three-way ANOVA on the measures of non-reinforced responses and peak time. On non-reinforced responses, the drug treatments was significant ($F_{(5,260)} = 49.9$, $p < 0.001$) while the three-factor interaction was also significant ($F_{(5,260)} = 2.25$, $p < 0.01$). This verifies a differential effect of D1 and D2 receptor antagonist in each of the three brain regions on the non-reinforced responses. On peak time, the drug treatment main effect was significant ($F_{(5,260)} = 69.3$, $p < 0.001$). The three-factor interaction was not significant, but the two-factor interaction between drug treatment and DA receptor subtype was significant ($p < 0.001$). This fits with our observation that D2 receptor antagonist uniformly failed to reverse the systemic AMP's timing effects in all three brain regions, while D1 receptor antagonist reversed systemic AMP's timing effect in all three brain regions (Table 2).

3.6. Comparison of mean imputation and stochastic regression imputation

Additionally, we conducted stochastic regression imputation to replace the missing data in the following three groups – mPFC D1, NAC D1 and NAC D2 groups. As shown in Table 3, the results are quite similar between these two imputation methods. Although the mean imputation method could underestimate the group variance in the three groups with missing data rate higher than 10%, we found that a more robust imputation method also yielded very similar results. Thus, our interpretation of the entire data is still valid.

4. Discussion

Consistent with our previous reports [9,26], the current study shows that systemic injection of AMP is able to profoundly increase non-reinforced responses and decrease reinforced responses in the DRL task. This results in a leftward shift of the IRT response curve that can be attributed to either a deficit in impulsive control or a faster internal clock speed for timing. Both accounts lead to responding prematurely with the increase of non-reinforced responses before the criterion time and a shorter peak time from the IRT curve. Premature (non-reinforced) responses are counter-productive because they reduce the maximal amount of reinforcers that could be obtained in the DRL task. It should be noted that AMP-treated rats do remain responsive, but just with degraded timing and poor impulsive control [33,34]. To further explore into the neural substrates underlying these timing-associated premature responses, this study is the first to conduct a larger-scale survey using intra-cranial microinjection of SCH and RAC into three major dopaminergic terminals with the aim to pinpoint the roles of the D1 and D2 receptor subtypes that may underlie the influence of AMP during DRL behavior, namely the stimulant drug induced timing impulsivity.

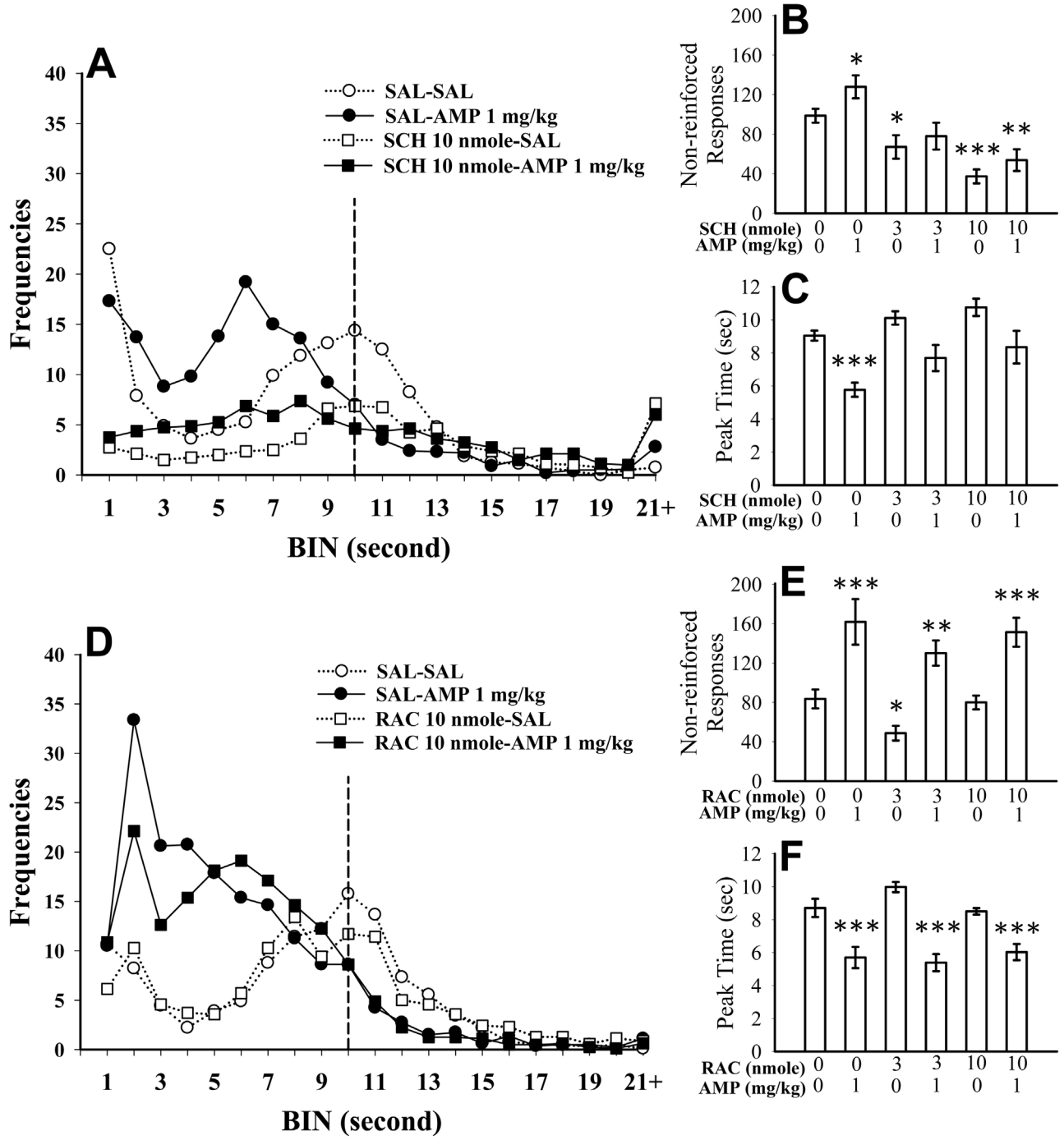

Fig. 3. The effects of SCH23390 (SCH, A–C) and raclopride (RAC, D–F) locally infused in the nucleus accumbens (NAC) on d-amphetamine (AMP) induced behavioral changes in the DRL–10 s task (conventions as in Fig. 2). Asterisks denote significant differences in the Fisher LSD *post hoc* comparisons between the indicated drug treatment and the SAL–SAL condition. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

The D1, but not D2, receptors in all three brain regions tested are involved in the effects of systemic AMP injection in both impulsivity and timing (Table 2). Note that SCH alone (at a high dose) was also observed to significantly reduce the non-reinforced responses, rendering better impulsive control. On the other hand, the same drug alone had no effect in reducing reinforced responses (see Table 1A–C, left columns). Thus, the speculation that SCH microinjection into these three brain regions simply reduced general motivation or overall motor output was not the case. That is, the motor requirement and the motivation to obtain reinforcement in the DRL procedure were still preserved with SCH microinjection. In addition, infusing a high dose of SCH into these three sites, when combined with systemic AMP injection, significantly reversed the peak time decreased by AMP alone. This suggests that the D1 receptor blockade by itself in all the three brain regions not only leads to better impulsivity control, but it can also counteract the clock speed effect created by AMP. Unlike SCH, RAC did not produce any significant effect on impulsivity nor timing with respect to DRL behavior in these three regions either alone or in combination with AMP, except in one group and in one measure – mPFC, in which it reversed the AMP's effect on impulsivity. This suggests a weak role for D2 receptors in the NAC and dHIP regarding these behavioral responses, at least in the dose rage (3–10 nmol) tested. Interestingly, using the 5-CSRT task, Pattij and associates [35] reported that eticlopride (a D2 receptor antagonist) infused into the NAC

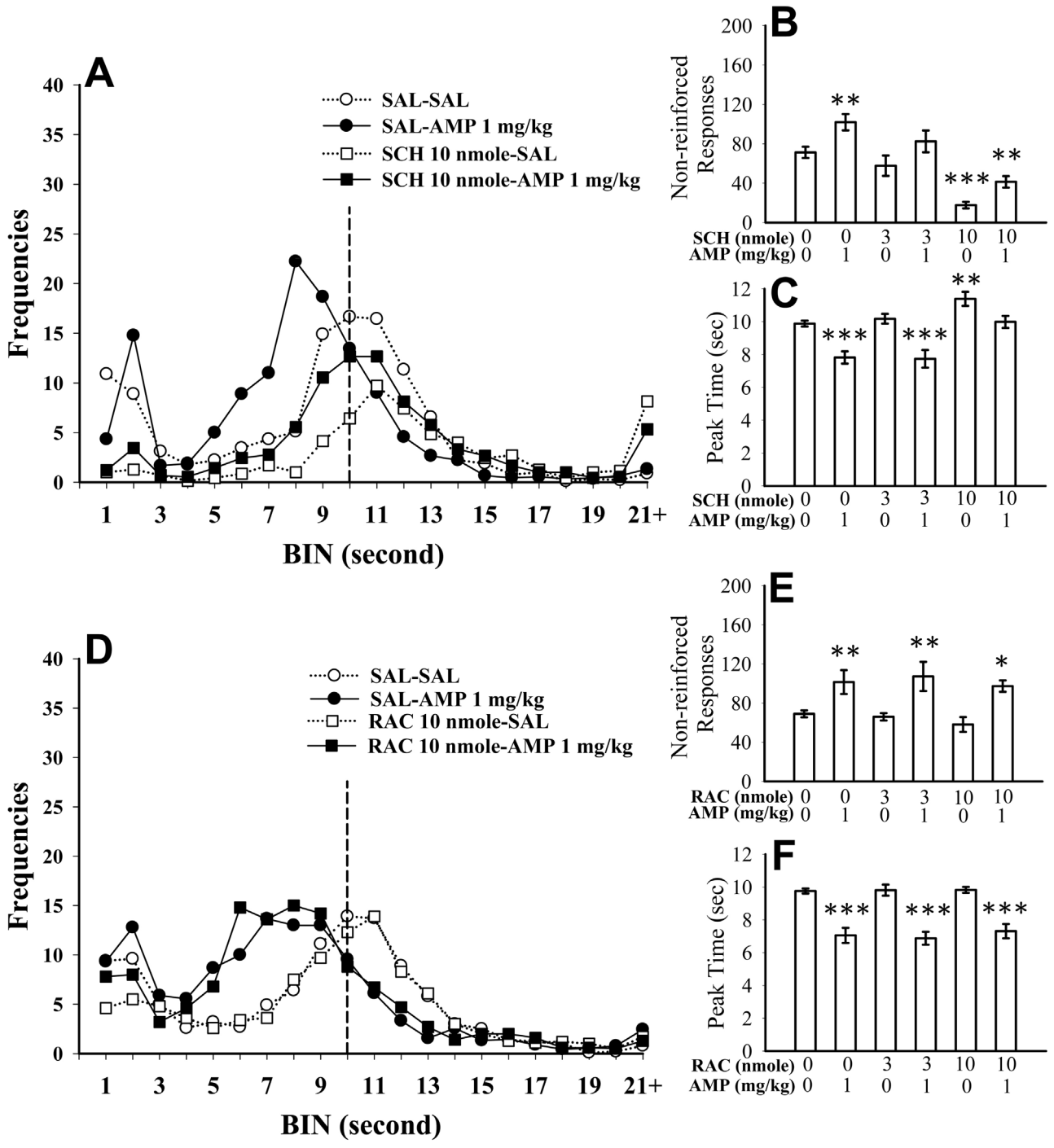

Fig. 4. The effects of SCH23390 (SCH, A-C) and raclopride (RAC, D-F) microinjected into the dorsal hippocampus (dHIP) on d-amphetamine (AMP) induced behavioral changes in the DRL–10 s task (conventions as in Fig. 2). Asterisks denote significant differences in the Fisher LSD *post hoc* comparisons between the indicated drug treatment and the SAL–SAL condition. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

produced a more robust reversal effect on the impulsive control deficits induced by systemic AMP injection than SCH. This disparity for the NAC may be attributed to the different tasks used, which measured different facets of impulsivity (e.g. timing in DRL vs. waiting in 5-CSRT) or to the different doses of drugs used (AMP – 0.5 vs. 1.0 mg/kg here and eticlopride 2.6 nmol vs. RAC 10 nmol here).

The mPFC has been shown to be involved in the regulation of the clock effect using other interval timing tasks [36] as well as during response inhibition experiments [23]. Distinctive from the data in the NAC and dHIP, both D1 and D2 receptors are involved in modulating the effects of AMP on impulsivity in the mPFC, and mPFC D1 in particular is involved in timing. Regarding the role of timing in the mPFC, our mPFC data is consistent with previous findings showing that aspiration lesions of the frontal cortex abolished the modulatory effect of methamphetamine on clock speed [36]. Moreover, we showed that only D1, but not D2, signaling in the mPFC is more important in timing, consistent with recent studies [e.g.,[37]]. A “top-down” role has been argued for the mPFC in impulsive action as tested by the 5-CSRT based on lesions in this area [38] and functional disconnection of the mPFC-NAC pathway [39]. And, only limited evidence for the mPFC being involved in stopping impulsivity is noted [40].

This study extended the operant psychopharmacology of AMP on

Table 2
Summary of the effects of SCH23390 and raclopride locally infused into three selected brain areas on d-amphetamine (AMP; 1.0 mg/kg, i.p.) induced behavioral changes using the DRL–10 s task to assess impulsive control and timing.

	D1 antagonist (SCH23390)		D2 antagonist (raclopride)	
	Impulsivity	Timing	Impulsivity	Timing
mPFC	Reversed[1]/Reduced[2]	Reversed	Reversed	Failed to reverse[3]
NAC	Reversed/Reduced	Reversed	Failed to reverse	Failed to reverse
dHIP	Reversed/Reduced	Reversed	Failed to reverse	Failed to reverse

Note: 1) "Reversed" indicates that the antagonist when infused into the corresponding brain region successfully reversed the behavioral changes induced by systemic injection of AMP. 2) "Reduced" indicates that the antagonist by itself successfully reduced the level of impulsivity (or the non-reinforced responses) when infused into the corresponding brain region. 3) "Failed to reverse" indicates that it is confirmed by statistics that the antagonist was not able to reverse the behavioral changes induced by systemic injection of AMP.

DRL behavior [20]. The present findings show that there are dissociable region-dependent effects of the DA receptor antagonists on DRL behavior altered by AMP. These findings have extended our understanding of the neural substrates involved in DRL behavior and compliment to previous reports on mPFC [41,42], NAC [43–45], and dHIP [42,46]. More importantly, unlike approaches such as regional inactivation (e.g. by muscimol) or neurotoxic lesions, our approach is more specific because it is able to determine which DA receptor subtypes in which brain regions contributes to the behavioral changes induced by systemic AMP injection. While AMP may stimulate noradrenergic (or serotoninergic) system in conjunction with dopamine, when a DA specific receptor subtype antagonist, via intra-cranial infusion, is able to reverse the behavioral effects of systemic AMP, the involvement of DA is straightforward. Despite this, it should be noted that SCH23390 also has relatively high affinity for 5-HT2a and 5-HT2c receptors. Future studies can further explore the effect of SCH39166 (ecopipam) that is shown to have relatively low affinity to 5-HT receptors and remains highly selective for D1 receptors [47–49].

The effects of AMP on the DRL procedure are comparable to, but distinctive from, those obtained using other tasks measuring impulsive action including the 5-CSRT, the simple reaction time, the stop-signal, and the go/no-go tasks [4]. Behaviorally, as compared to these four motor-based paradigms of impulsive action that can be used to test the impulsivity on "waiting" [2,50] or "stopping" [40,51], the present DRL procedure along with the quantitative analyses of IRT data (especially the peak time) can be used to characterize a combination of timing and impulsive control, or the idea of timing impulsivity. That is, the timing impulsivity requires an internal representation of the passage of time in order to guide the behavior without any external cues. From clinical studies, impairment of timing impulsivity is characteristics of patients with ADHD [52,53] or stimulant drug addiction [54]. Hence, a deficit in timing impulsivity could result from the imbalance of DA signaling

Table 3
Comparisons of mean imputation and stochastic regression imputation on mPFC D1, NAC D1 and D2 data sets.

(A) Medial Prefrontal Cortex (mPFC) D1 group (n = 10)

	Mean imputation			Stochastic regression imputation	
	Non-reinforced Response	Peak Time	Missing data	Non-reinforced Response	Peak Time
SAL-SAL	68.0 ± 12.	9.93 ± 0.34	0	68.0 ± 12.	9.93 ± 0.3
SAL-AMP	*132.5 ± 18.7	*6.17 ± 0.60	0	*132.5 ± 17.0	*6.17 ± 0.60
Low-SAL	80.2 ± 13.	9.51 ± 0.18	0	80.2 ± 13.	9.51 ± 0.18
Low-AMP	*113.2 ± 15.8	*6.26 ± 0.38	1	*107.6 ± 16.8	*6.53 ± 0.47
High-SAL	*35.4 ± 4.0	10.9 ± 0.30	5	65.4 ± 14.0	10.7 ± 0.76
High-AMP	44.0 ± 7.3	10.8 ± 0.90	5	52.4 ± 13.2	10.7 ± 1.03

(B) Nucleus Accumbens (NAC) D1 group (n = 10)

	Mean imputation			Stochastic regression imputation	
	Non-reinforced Response	Peak Time	Missing data	Non-reinforced Response	Peak Time
SAL-SAL	98.6 ± 7.0	9.04 ± 0.3	2	90.1 ± 9.6	8.64 ± 0.40
SAL-AMP	*127.9 ± 11.6	*5.77 ± 0.43	0	*127.9 ± 11.6	*5.77 ± 0.43
Low-SAL	*67.1 ± 12.	10.1 ± 0.40	0	67.1 ± 12.	10.1 ± 0.40
Low-AMP	75.1 ± 14.	7.56 ± 0.80	1	87.9 ± 17.	7.76 ± 0.80
High-SAL	*37.3 ± 6.9	10.7 ± 0.52	3	*30.2 ± 8.0	*11.2 ± 0.70
High-AMP	*53.8 ± 10.9	8.34 ± 0.99	2	*51.8 ± 11.1	8.02 ± 1.01

(C) Nucleus Accumbens (NAC) D2 group (n = 9)

	Mean imputation			Stochastic regression imputation	
	Non-reinforced Response	Peak Time	Missing data	Non-reinforced Response	Peak Time
SAL-SAL	83.6 ± 9.6	8.70 ± 0.56	0	83.6 ± 9.6	8.70 ± 0.60
SAL-AMP	*161.9 ± 23.2	*5.70 ± 0.64	1	*165.0 ± 23.4	*5.44 ± 0.69
Low-SAL	*48.7 ± 7.5	9.98 ± 0.31	2	*41.5 ± 9.2	*10.2 ± 0.40
Low-AMP	*130. ± 12.9	*5.39 ± 0.52	2	*118. ± 15.7	*5.36 ± 0.58
High-SAL	80.0 ± 7.0	8.49 ± 0.20	2	74.0 ± 8.2	8.43 ± 0.40
High-AMP	*151. ± 14.7	*6.03 ± 0.49	1	*145. ± 16.1	*5.84 ± 0.53

Note: Two quantitative measures of the DRL–10 s performance – Non-reinforced response and peak time are listed here to illustrate the difference between mean imputation and stochastic regression imputation in replacing the missing data. The two imputation methods yielded very similar results, although not identical. Nevertheless, the minor difference does not change our interpretation of the original data with mean amputation. (A) data from the mPFC group with SCH treatment; (B) data from the NAC group with SCH treatment; and (C) data from the NAC group with RAC treatment. The data points with significant Fisher LSD *post-hoc* test results in comparison with the SAL–SAL condition are denoted with a "*". Data are represented as Mean ± S.E.M.

within the mesocorticolimbic circuit [23]. Together, with the current data, timing impulsivity appears to be a distinctive form among the multifaceted domain of impulse behavior. As noted in a recent review [55], the hypothetically distinctive neural and psychological mechanisms that underlie each of the multiple forms of impulsivity should be further fractionated via the use of different tools or approaches, behaviorally including the DRL procedure. Intriguingly, a recent study reported that the DRL behavior task can be used to differentiate high versus low degree of impulsivity for investigating the underlying dopaminergic mechanisms [56].

In conclusion, the present study demonstrated a rodent behavioral model for studying timing impulsivity using the DRL procedure, in which the deficit of timing associated impulsive control was induced by systemic injection of AMP. With the local infusion of selective D1 and D2 receptor antagonists, we discovered dissociable brain region-dependent effects of DA receptor subtypes on timing process and impulsive responses that are altered by AMP on DRL behavior. This pattern of results in regarding to the stimulant-induced timing impulsivity supports the notion that the mesocorticolimbic DA system is important for timing impulsivity, and further provides evidence to advance our understanding of the neural mechanisms underlying the impulsive action.

Conflict of interest

The authors declare no conflict of interest.

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