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ORIGINAL INVESTIGATION

Intact discrimination reversal learning but slowed responding to reward-predictive cues after dopamine D1 and D2 receptor blockade in the nucleus accumbens of rats

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Abstract
Rationale The prediction error hypothesis of dopamine action states that dopamine signals are necessary for the brain to update the predictive significance of cues. Yet, little is known whether D1 or D2 receptor-mediated signals in the nucleus accumbens core (AcbC) are required to learn a reversal of the predictive significance of cues.
Objective Here we examined the effects of a selective D1 or D2 receptor blockade in the AcbC on learning a reversal of previously acquired cue–reward magnitude contingencies.
Materials and methods Rats were trained on a reaction time (RT) task demanding conditioned lever release with discriminative visual cues signalling in advance the upcoming reward magnitude (one or five food pellets). After acquisition, RTs were guided by cue-associated reward magnitudes, i.e. RTs of responses were significantly shorter for expected high vs low reward. Thereafter, cue–reward magnitude contingencies were reversed. Reversal learning was tested for 12 daily sessions with intra-AcbC micro-infusions being given on sessions 1–6. Subjects received pre-trial infusions of the selective D1 or D2 receptor antagonists, SCH23390 (0.5, 2 μg per side) or raclopride (1, 4 μg per side), or vehicle (0.5 μl).
Results Intra-AcbC infusion of SCH23390 (0.5, 2 μg) or raclopride (1, 4 μg) did not inhibit discrimination reversal learning, but the higher dose of each drug increased RTs of instrumental responses.
Conclusions In a visual discrimination task as used here, D1 and D2 receptor-mediated signals in the AcbC seem to be unnecessary in updating the reward-predictive significance of cues, rather, they serve to activate instrumental behaviour.

Keywords Instrumental conditioning · Reversal learning · Dopamine · Prediction error · Raclopride · SCH23390 · Rat

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Introduction

A growing body of evidence from studies in humans (Knutson and Cooper 2005) and experimental animals (Kelley et al. 2005) implicates the nucleus accumbens (Acb) in using information acquired by associative learning. Neurophysiological recordings in sub-human primates and rodents revealed that Acb neurons respond to learned cues that predict biologically significant outcomes and the outcomes themselves (Carelli et al. 2000; Schultz et al. 2003; Setlow et al. 2003; Woodward et al. 1999; Yun et al. 2004a). Likewise, behavioural studies suggest that the Acb plays a major role in the use of cues that predict the occurrence of biologically significant events to guide or modulate behaviour (Cardinal et al. 2002; Giertler et al. 2003; Hauber et al. 2000; Schoenbaum and Setlow 2003; Yun et al. 2004a).

Responding to reward-predictive cues critically depends on dopamine (DA) signalling in the Acb. For instance, studies using fast-scan cyclic voltammetry demonstrated that cues that signal the opportunity to respond for sucrose evoked a transient DA release in the Acb (Roitman et al. 2004). DA acts on at least five receptors classified as "D1-like" (D1/D5) or "D2-like" (D2, D3, D4) based on their

pharmacological profiles (e.g. Sokoloff et al. 1992). To date, most studies were directed to the role of D1 and D2 receptors in responding to reward-predictive cues. For instance, Nicola and colleagues showed that an intra-Acb blockade of D1 or D2 receptors abolished the influence of reward-predictive cues on Acb neuronal activity and reduced behavioural responding to cues (Yun et al. 2004a, b). However, these reports examined how DA signalling in the Acb govern animals' performance and its guidance by learned reward-predictive cues, rather than the role of Acb DA signalling to acquire cue–outcome contingencies or to adapt behaviour according to changes in cue–outcome contingencies. One of the few available studies revealed that in discrimination tasks where subjects must learn to respond to a change of the original place–reward pairings, destruction of DA terminals in the Acb disrupted reversal learning (Louilot et al. 1989). Learning of appetitive predictions under reversal conditions probably requires a prediction error signal that indicates the discrepancy between actually received reward and its prediction as suggested by models of temporal difference learning (Schultz 2006; Sutton and Barto 1990). Recent studies suggest that DA neurons emit prediction error signals (Schultz 2006) and indicate the presence of such signals in target areas of DA neurons such as the Acb or the prefrontal cortex (McClure et al. 2003; O'Doherty 2003). These findings imply that Acb DA signals are necessary to update the predictive significance of cues during reversal learning.

The aim of the current study was to test this hypothesis and to explore whether D1 and D2 receptor-mediated signals in the core sub-region of Acb (Zahm 2000) are essential for reversal learning. To this end, rats were trained in a reaction time (RT) task demanding conditioned lever release with predictive cues signaling in advance the upcoming reward magnitude (one or five pellets) (Giertler et al. 2005). After acquisition of the task, RTs of responses with expectancy of a high vs low reward magnitude were significantly shorter indicating that instrumental responding was guided by reward-predictive cues. Thereafter, we reversed the cue–reward contingencies and rats received intra-AcbC infusions of saline or of selective D1 or D2 receptor antagonists. If D1 or D2 receptors in the AcbC transmit a prediction error signal that shapes reversal learning, we expected a learning impairment after DA receptor blockade.

Using several measures, this task allows a detailed analysis of drug effects on instrumental behavior guided by reward-predictive stimuli. Response latencies were measured by RT, a parameter that is sensitive to drug-induced motor effects on responses initiation. In addition, during learning RTs become shorter for expected high vs low reward. Therefore, the RT differences of responses for expected low and high rewards are a sensitive index of discriminative learning of cue-associated reward values. The speed of response execution was measured by movement time (MT), a parameter that allows us to detect drug-induced motor effects. Response accuracy measured by the number of responses necessary to reach a fixed criterion of correct responses was used as an index of learning the instrumental contingency. Incorrect, i.e. premature or delayed responses, permitted to further assess drug effects on response preparation.

Materials and methods

Animals

Ninety-six Lister Hooded rats (Harlan Winkelmann, Borchen, Germany) were housed in transparent plastic cages (55×39×27 cm, Ferplast, Nürnberg, Germany). Temperature (20±2°C) and humidity (50–60%) in the animal house were kept constant and a 12:12-h light–dark schedule was used with lights on between 19:00 h and 7:00 h. Rats were given ad libitum access to water; food was restricted to 15 g per animal and day. On days without behavioral testing, rats received 15 g standard laboratory maintenance chow (Altromin, Lage, Germany). On days with behavioral tests, rats received in the testing apparatus 5.4 g food pellets as reward (45 mg pellets, Bioserv, Frenchtown, USA). On these days, the amount of standard laboratory chow given was reduced to 9.6 g per animal. Rats weighed 200–210 g on arrival and 250–270 g at the time of surgery. All animal experiments were conducted according to the German Law on Animal Protection and approved by the proper authorities in Stuttgart, Germany.

Surgery

For stereotaxic surgery, animals were anaesthetized with ketamine (120 mg/kg i.m.) (Bela-Pharm GmbH, Vechta, Germany) and xylazine (4 mg/kg i.m.) (Bayer AG, Leverkusen, Germany) and secured in a Kopf stereotaxic apparatus (Kopf Instruments, Tujunga, USA). Bilateral 15 mm stainless steel guide cannulae with an outer diameter of 0.8 mm were aimed at the AcbC and implanted using standard stereotaxic procedures. The coordinates were: 3.4 mm anterior bregma, ±1.9 mm lateral to midline, and 5.3 mm ventral from the skull with the toothbar 5 mm above the interaural line. The guide cannulae were occluded by stainless steel stylets. Each rat was given at least 5 days to recover from surgery before behavioral testing was started.

Drug injection

Animals received bilateral intra-AcbC injections of the D1 receptor antagonist R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepinhydro-chloride (SCH23390, Research Biochemicals, Natick, USA) (2 or 0.5 μg in 0.5 μl 0.9% sterile saline), the D2 receptor antagonist raclopride (Sigma-Aldrich Chemie GmbH, Steinheim, Germany) (4 or 1 μg in 0.5 μl 0.9% sterile saline) or vehicle (0.5 μl 0.9% sterile saline). The doses of SCH23390 and raclopride were based on pilot studies and data reported in the literature. The higher doses of both drugs used here were highly effective after intra-Acb micro-infusion, but largely devoid of gross motor effects (e.g. Hernandez et al. 2005; Nicola et al. 2005; Wakabayashi et al. 2004; Yun et al. 2004a).

On injection days, the stainless steel stylets were removed and the injection cannulae (outer diameter: 0.45 mm, length: 18 mm) were lowered to the final site of infusion and attached via polyvenylchloride tubing to microliter syringes controlled by a syringe pump (Med Associates, St. Albans, VT, USA). Drugs were delivered over a 1-min interval and the injection cannulae were left in position for a further minute to allow for diffusion. After injection, each rat remained in its home cage for an additional 10 min before being placed in the test chamber.

Apparatus

Four experimental chambers (24×21×30 cm) (Med Associates, St. Albans, VT, USA) were used. Each chamber was supplied with a retractable lever, two cue lights (one above the retractable lever, the other above the food receptacle) and encased in a sound attenuating cubicle with a fan providing a constant low level of background noise. Each food receptacle was equipped with an infrared head entry detector. The experiments were controlled online by a Windows 98™ based computer system equipped with SmartControl®-Interfaces and the MedPC™-Software (Med Associates, St. Albans, VT, USA).

RT task

A simple RT task as used in previous studies (Giertler et al. 2005) was employed. The task demands conditioned lever release with instructive cues indicating the reward magnitude to be obtained after a subsequent imperative cue. Rats had to press the lever and to wait for the imperative cue, which was provided by the cue light above the lever after a foreperiod of 0.3 s. The imperative cue signalled to the rats to release the lever quickly and to respond to the food receptacle in which the food pellets were delivered (45 mg pellets, Bioserv, Frenchtown, USA). On each correct trial, the rats received either one or five food pellets. The number of pellets for each trial was pseudo-randomly determined in advance and signalled to the rats by two distinct brightness levels of the cue lights (220 lx or 30 lx, 1 cm distance, measured by a light sensor FL A613-VL; Ahlborn, Holzkirchen, Germany with a data acquisition system Almeno 2290-8; Ahlborn, Holzkirchen, Germany), which provide the instructive cues. After the inter-trial interval of 3 s, the instructive cue was turned on at the beginning of each trial 3 s before lever insertion and remained present until delivery of the food reward. Brightness levels of instructive cues were balanced, i.e. for 50% of the rats a bright cue was associated with the delivery of five pellets and a dim cue was associated with the delivery of one pellet. For the other 50% of the rats, the opposite pattern was used.

Reaction time (RT) is defined as the latency from the onset of the imperative cue to lever release and movement time (MT) is defined as the latency from lever release to photobeam disruption in the food receptacle were recorded with an accuracy of <10 ms. For a correct trial, animals had to release the lever within RT<2 s after presentation of the imperative cue. Responses before the onset of the imperative cue presentation were defined as "early" responses, responses with RT≥2 s were defined as "late" responses. A daily individual session demanded 40 correct trials, i.e. 20 correct trials for each reward magnitude (one and five pellets). A simplified scheme on the order of trial events is given in Fig. 1.

Experimental procedure

Experiment 1 examined the effects of an intra-AcbC D1 receptor antagonism, experiment 2 the effects of an intra-AcbC D2 receptor antagonism on discrimination reversal learning. The design of both experiments was identical. Different groups of rats were trained in the RT task described above; acquisition was tested throughout 6 days with one daily session. Thereafter, cue–reward magnitude contingencies were reversed and reversal learning was analyzed throughout 12 days within one daily session; during the first 6 days animals received micro-injections of either vehicle, SCH23390 or raclopride.

1. *Pre-operative habituation.* In the first two sessions, the subjects were habituated to the experimental chamber with access to food pellets placed into the food receptacle. In the following five sessions, a habituation program with a fixed ratio-1 schedule commenced until a criterion of 20 consecutive lever responses was attained. Afterwards, rats were subjected to surgery.
2. *Acquisition.* After post-operative recovery the experiment was started with one daily session; data from the

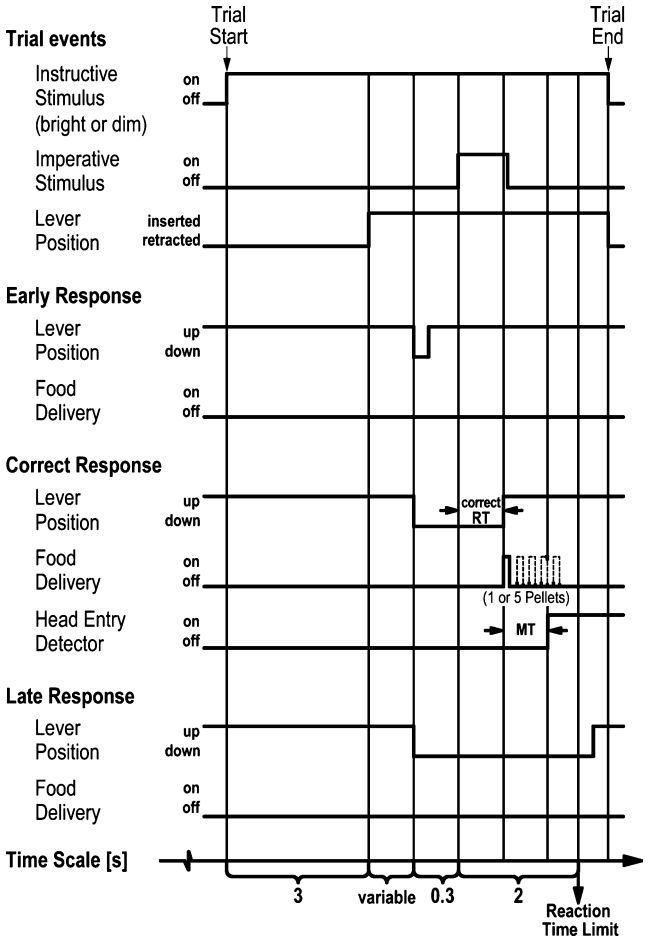

Fig. 1 Schematic representation of the order of trial events. First, an instructive stimulus was turned on at one of two brightness levels indicating the upcoming reward magnitudes (one or five pellets). Thereafter, the rat pressed the inserted lever spontaneously. After the foreperiod of 0.3 s, the imperative stimulus signalled the animal to release the lever. Responses with RT<2 s were considered as being correct and were rewarded. Early responses initiated before the onset of the imperative stimulus or late responses (RT≥2 s) caused the trial to be repeated

initial session were not evaluated. During days 1–6 task acquisition was examined. In each session, animals received a sham injection procedure including handling procedure, insertion of injection cannulae dummies and operation of the injection pump (without running an injection) before the onset of individual behavioural testing.

3. *Reversal.* Subsequently, learning of reversed cue–reward magnitude contingencies was tested on days 7–18, i.e. rats had to learn that the cue formerly predicting high reward magnitude was associated with low reward magnitude and vice versa. On days 7–12, i.e. the first six out of 12 sessions under reversal conditions, rats received a drug or vehicle micro-injection (4 μg raclopride, n=16, vehicle n=15; 1 μg raclopride, n=8, vehicle, n=7; 2 μg SCH23390, n=16; vehicle, n=16; 0.5 μg SCH23390, n=8, vehicle, n=8) before the onset of behavioral testing. No drugs were given on days 13–18; to exclude an impact of the handling procedure used for micro-injections, all animals were exposed to the handling procedure in these latter sessions. Two animals of experiment 2 were excluded due to guide cannula occlusion.

Data analysis

In line with earlier studies (e.g. Bohn et al. 2003), the subjects perceived brightness levels of instructive cues equally, i.e. for a given reward magnitude level, the mean accuracy and RT/MT values obtained with a bright or a dim cue did not differ significantly (data not shown). Therefore, response measures for a given reward magnitude obtained with bright and dim instructive stimuli were collapsed.

Data are expressed as means from blocks of three sessions. Furthermore, the standard error of the differences (SED) was used for the presentation of descriptive statistics to provide an estimate of the population variance for between-group comparisons. The SED derived from the appropriate ANOVA term was calculated by using the formula provided in Cochran and Cox (1957).

The overall number of trials (early+correct+late responses) to reach the criterion of 40 correct responses (20 per reward magnitude) was used as an index of the accuracy of performance. The calculations on RT and MT performance were conducted with data from correct trials (RT<2 s). When averaging RT and MT data, a geometric mean was calculated for each rat and session, as the geometric mean is less influenced by outlying data points than the arithmetic mean. Overall, RT and MT means of responses associated with the high and low reward magnitudes represent the arithmetic average of the geometric means of individual rats (Brasted et al. 1997). In addition, we calculated RT differences of responses for expected low and high rewards ($RT_{low\ reward}$–$RT_{high\ reward}$) as an index of discriminative learning of cue-associated reward values.

Data from experiments 1 and 2 were subjected to separate repeated measures analysis of variance (ANOVA). Numbers of correct and early responses, RTs and MTs of correct responses during acquisition (blocks 1–2) were compared using an ANOVA with group (groups to be treated with vehicle, raclopride or SCH23390 during reversal) as between-subjects factors, and reward magnitude and blocks as within-subjects (repeated measures) factors. Likewise, numbers of correct and early responses, RTs and MTs of correct responses during reversal were compared using separate ANOVA for treatment blocks

(3–4) and post-treatment blocks (5–6) with group (groups treated with vehicle, raclopride or SCH23390) as between-subjects factors, and reward magnitude and blocks as within-subjects factors. All statistical computations were carried out with STATISTICA™ (version 7.1, StatSoft®, Inc., Tulsa, OK, USA). The level of statistical significance (α-level) was set at $p<0.05$.

Histology After completion of behavioral testing, animals were euthanized by an overdose of sodium pentobarbital (150 mg/ kg, i.p.) (Sigma-Aldrich, Taufkirchen, Germany) to control for correct placement of cannulae. Brains were rapidly removed, fixed in 10% formalin for 2.5 h and stored in 30% glucose. Brain sections (30 μm) were cut with a cryostat (Reichert & Jung, Heidelberg, Germany), mounted on coated slides and stained with cresyl violet. The locations of the micro-infusion cannulae tips are presented in Fig. 2. No animal had to be excluded due to cannulae misplacement. The possibility that some of the effects observed in our study may be due to drug diffusion into the adjacent shell sub-region cannot be discounted. However, the exact amount of spread of drugs from the site of infusion in the AcbC is not known as studies with radiolabeled SCH23390 and raclopride would be required. Previous studies comparing core vs shell micro-infusions of SCH23390 and raclopride revealed relatively small differences in the effects on lever pressing (Nowend et al. 2001). Thus, from these data it is difficult to delineate whether one or both Acb sub-regions contribute to the observed behavioural effects and to assess the role of drug diffusion. However, other studies showed differential behavioural effects after core and shell micro-injections of glutamate receptor antagonists in the same volume as used here (Di Ciano and Everitt 2001) suggesting that the spread of drugs appears to be rather limited.

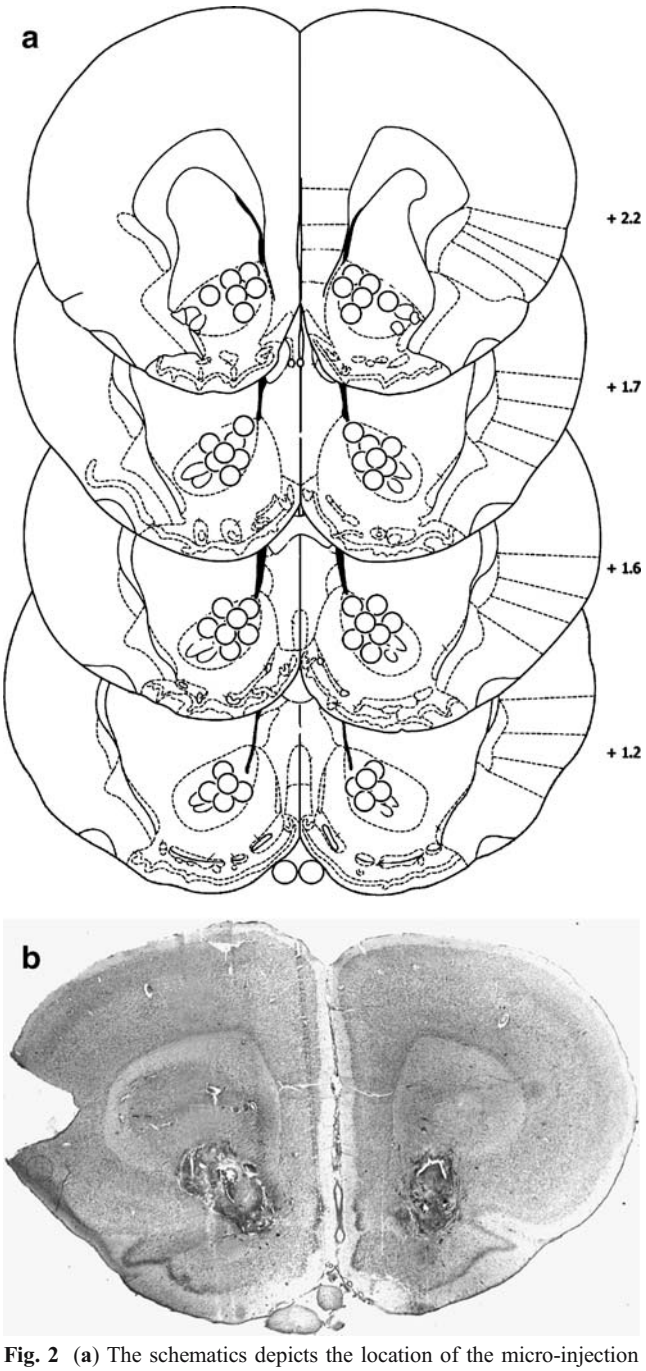

Fig. 2 (**a**) The schematics depicts the location of the micro-injection cannulae tips (outer diameter 0.45 mm; • symbols are drawn to scale) in the AcbC. The number of symbols does not match the total number of rats included in the behavioural analyses because numerous cannulae tip placements were overlapping and one symbol thus represents more than one cannula tip placement. Plates are adaptations from the atlas of Paxinos and Watson (1997). Numbers beside each plate correspond to millimeters anterior to bregma. (**b**) Nissl stain of a coronal section indicating the cannualae tip placement

Results

In all experiments, the animals were divided into two treatment groups to be treated with vehicle or drugs according to their performance during acquisition. The groups were chosen so that no significant difference of RT was detectable during acquisition ($F<1$).

Experiment 1: effects of an intra-AcbC D1 receptor blockade

Reaction times

SCH23390 (0.5 μg) During acquisition, RTs significantly decreased over blocks (main effect of blocks; $F_{(1,14)}=12.44$, $p<0.01$) and were guided by the expected reward magnitude (main effect of reward magnitude; $F_{(1,14)}=41.87$, $p<0.0001$) in animals to be treated with vehicle or SCH23390 (Fig. 3a). During reversal learning, RTs were

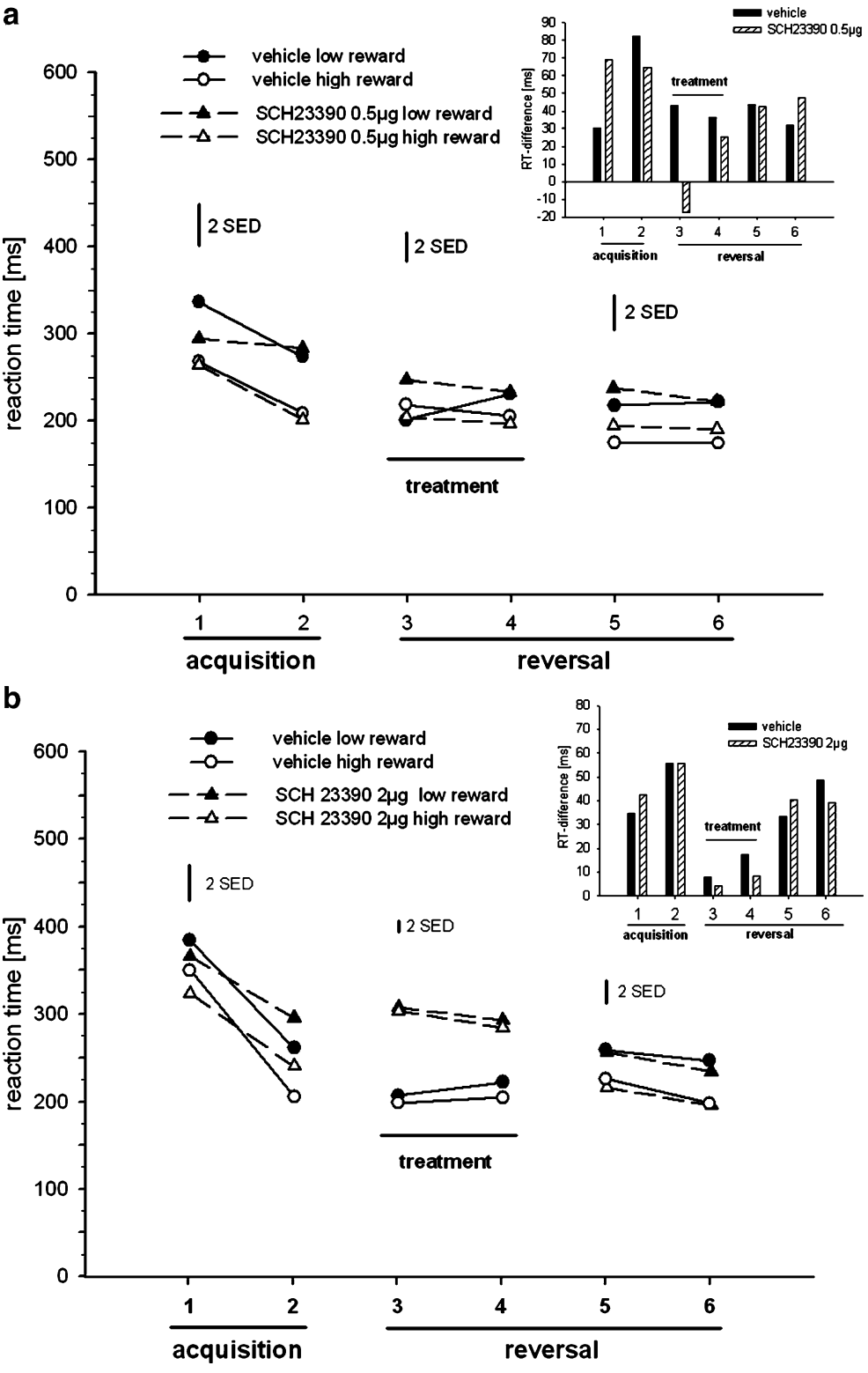

Fig. 3 Effects of intra-AcbC infusion of SCH23390 on RT. Mean RTs of correct responses in blocks of three sessions are given; SED bars represent two SEDs of the means. Insets: RT differences ($RT_{low\ reward}$–$RT_{high\ reward}$); i.e. positive values denote faster responding for expected high reward. (**a**) 0.5 µg SCH23390 (n=8) or vehicle (n=8) was given on blocks 3–4. RTs were significantly guided by expected reward on blocks 1–2, 3–4 and 5–6. Infusion of SCH2330 did not increase RTs on blocks 3–4. (**b**) 2 µg SCH23390 (n=16) or vehicle (n=16) was given on blocks 3–4. RTs were significantly guided by expected reward on blocks 1–2 and 5–6. In addition, infusion of SCH2330 produced a significant increase in RTs on blocks 3–4

guided by the expected reward magnitude on treatment blocks (main effect of reward magnitude; $F_{(1,14)}$=8.21, p<0.01; block×treatment×reward magnitude interaction ($F_{(1,14)}$=5.35, p=0.04), but there was no main effect of treatment. On post-treatment blocks, RTs depended on the expected reward magnitude ($F_{(1,14)}$=10.87, p<0.01).

Accordingly, during reversal learning starting on block 4, RT differences in both groups became positive, i.e. were faster for expected high reward (Fig. 3a, inset).

SCH23390 (2 μg) RTs significantly decreased over blocks 1–2 (main effect of blocks; $F_{(1,30)}$=43.84, p<0.0001) and were guided by the expected reward magnitude (main effect of reward magnitude; $F_{(1,30)}$=55.28, p<0.0001) in animals to be treated with vehicle or SCH23390 (Fig. 3b). RTs were no longer guided by the expected reward magnitude on blocks 3–4 in both treatment groups and increased in rats which received micro-injections of SCH23390. ANOVA revealed a significant main effect of treatment ($F_{(1,30)}$=16.69, p< 0.0001) and a significant block×treatment interaction ($F_{(1,30)}$=10.27, p<0.004), but no reward magnitude×treatment interaction. On blocks 5–6, RTs were guided by the expected reward magnitude in both groups. ANOVA revealed significant main effects of reward magnitude ($F_{(1,30)}$=36.18, p<0.0001) and blocks ($F_{(1,30)}$=6.69, p<0.02). During reversal learning, RT differences in both groups became increasingly positive (Fig. 3b, inset).

Movement times

SCH23390 (0.5 μg) MTs decreased during acquisition (main effect of blocks; $F_{(1,14)}$=9.39, p<0.01) in both groups as shown in Fig. 4a. On blocks 3–4, there was no main effect of treatment.

SCH23390 (2 μg) MTs decreased during acquisition (main effect of blocks; $F_{(1,30)}$=52.21, p<0.0001) in animals to be treated with vehicle or SCH23390 (Fig. 4b). There were no significant main effects of treatment on blocks 3–4.

Accuracy of performance

SCH23390 (0.5 μg) In line with previous studies with similar tasks (Giertler et al. 2005), rats needed approx. 50–60 trials to achieve the criterion of 40 correct responses (20 responses with RT<2 s for each reward magnitude). ANOVA on the number of trials to reach criterion on blocks 1–2 indicated no main effects of group. Also, there was no main effect of treatment on blocks 3–4. Likewise, ANOVA on the number of early responses indicated no significant group/treatment effects on blocks 1–2 and 3–4 (Fig. 5a).

SCH23390 (2 μg) ANOVA on the number of trials to reach criterion indicated no main effects of group on blocks 1–2 and treatment on blocks 3–4 (Fig. 5b). ANOVA on the number of early responses indicated a trend for a significant treatment effect on blocks 3–4 ($F_{(1,30)}$=3.45, p=0.07), while on blocks 1–2 no significant group effect was detected.

Experiment 2: effects of intra-AcbC D2 receptor blockade

Reaction times

Raclopride (1 μg) RTs significantly decreased over blocks 1–2 (main effect of blocks; $F_{(1,14)}$=19.42, p<0.001) and were guided by the expected reward magnitude (main effect of reward magnitude; $F_{(1,14)}$=51.96, p<0.0001) in animals to be treated with vehicle or raclopride. On blocks 3–4, RTs were not guided by the expected reward magnitude in both treatment groups. In addition, ANOVA revealed no significant main effect of treatment. On post-treatment blocks 5–6, RTs were guided by the expected reward magnitude in both groups. ANOVA revealed significant main effects of reward magnitude ($F_{(1,14)}$=18.03, p<0.001) and blocks ($F_{(1,14)}$=11.79, p<0.01). RT differences in both groups are shown in Fig. 6a (inset).

Raclopride (4 μg) As shown in Fig. 6b, RTs significantly decreased over blocks 1–2 (main effect of blocks; $F_{(1,29)}$= 7.17, p<0.02) and were guided by the expected reward magnitude (main effect of reward magnitude; $F_{(1,29)}$= 62.65, p<0.0001) in animals to be treated with vehicle or raclopride. On blocks 3–4, RTs were guided by the expected reward magnitude in both treatment groups (main effects of reward magnitude; $F_{(1,29)}$=14.21, p<0.0001, no reward magnitude×treatment interaction), but increased in rats which received micro-injections of raclopride (main effect of treatment; $F_{(1,29)}$=11.32, p<0.003). On blocks 5–6, RTs were also guided by the expected reward magnitude in both groups. ANOVA revealed significant main effects of reward magnitude ($F_{(1,29)}$=24.28, p<0.0001) and blocks ($F_{(1,29)}$=14.30, p<0.0001). Furthermore, results show that RT differences in both groups became increasingly positive during reversal learning (Fig. 6b, inset).

Movement times

Raclopride (1 μg) MTs significantly decreased during acquisition (main effect of blocks; $F_{(1,14)}$=7.15, p<0.02) in animals to be treated with vehicle or raclopride as shown in Fig. 7a. On treatment blocks 3–4, there was no significant main effect of treatment.

Raclopride (4 μg) MTs significantly decreased on blocks 1–2 (main effect of blocks; $F_{(1,29)}$=20.25, p<0.0001) in

animals to be treated with vehicle or raclopride as shown in Fig. 7b. On treatment blocks 3–4, there was no significant main effect of treatment.

Accuracy of performance

Raclopride (1 μg) ANOVA on the number of trials to reach criterion revealed a significant effect of blocks (main effect of blocks; $F_{(1,14)}=5.77$, $p=0.03$), but indicated no main effects of group on blocks 1–2. Likewise, there were no

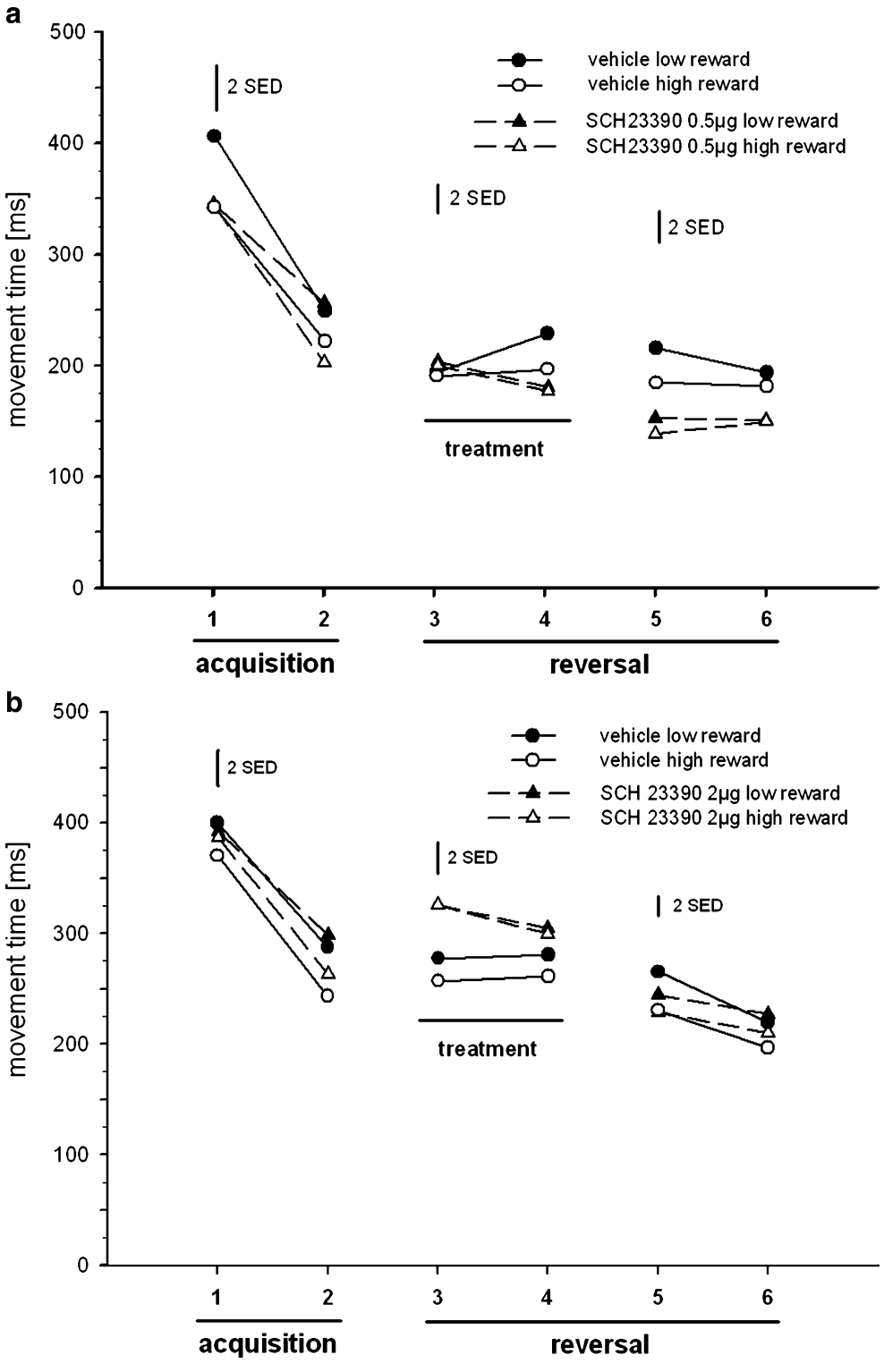

Fig. 4 Effects of intra-AcbC infusion of SCH23390 on MTs. Mean MTs of correct responses in blocks of three sessions are given; SED bars represent two SEDs of the means. (**a**) 0.5 μg SCH23390 ($n=8$) or vehicle ($n=8$) and (**b**) 2 μg SCH23390 ($n=16$) or vehicle ($n=16$) was given on blocks 3–4. Infusion of SCH23390 did not significantly affect MTs on blocks 3–4

main effects of treatment on blocks 3–4 (Fig. 8a). Furthermore, ANOVA on the number of early responses revealed a significant effect of group ($F_{(1,14)}$=5.77, p=0.03) on blocks 1–2, while on blocks 3–4 no significant treatment effects were detected.

Raclopride (4 μg) ANOVA on the number of trials to reach criterion on blocks 1–2 indicated no main effects of group. On blocks 3–4, there was a significant main effect of treatment. In addition, ANOVA on the number of early responses indicated a significant treatment effect ($F_{(1,29)}$= 7.67, p<0.01) on reversal blocks 3–4, while on blocks 1–2 and 5–6 no significant group effects were detected (Fig. 8b).

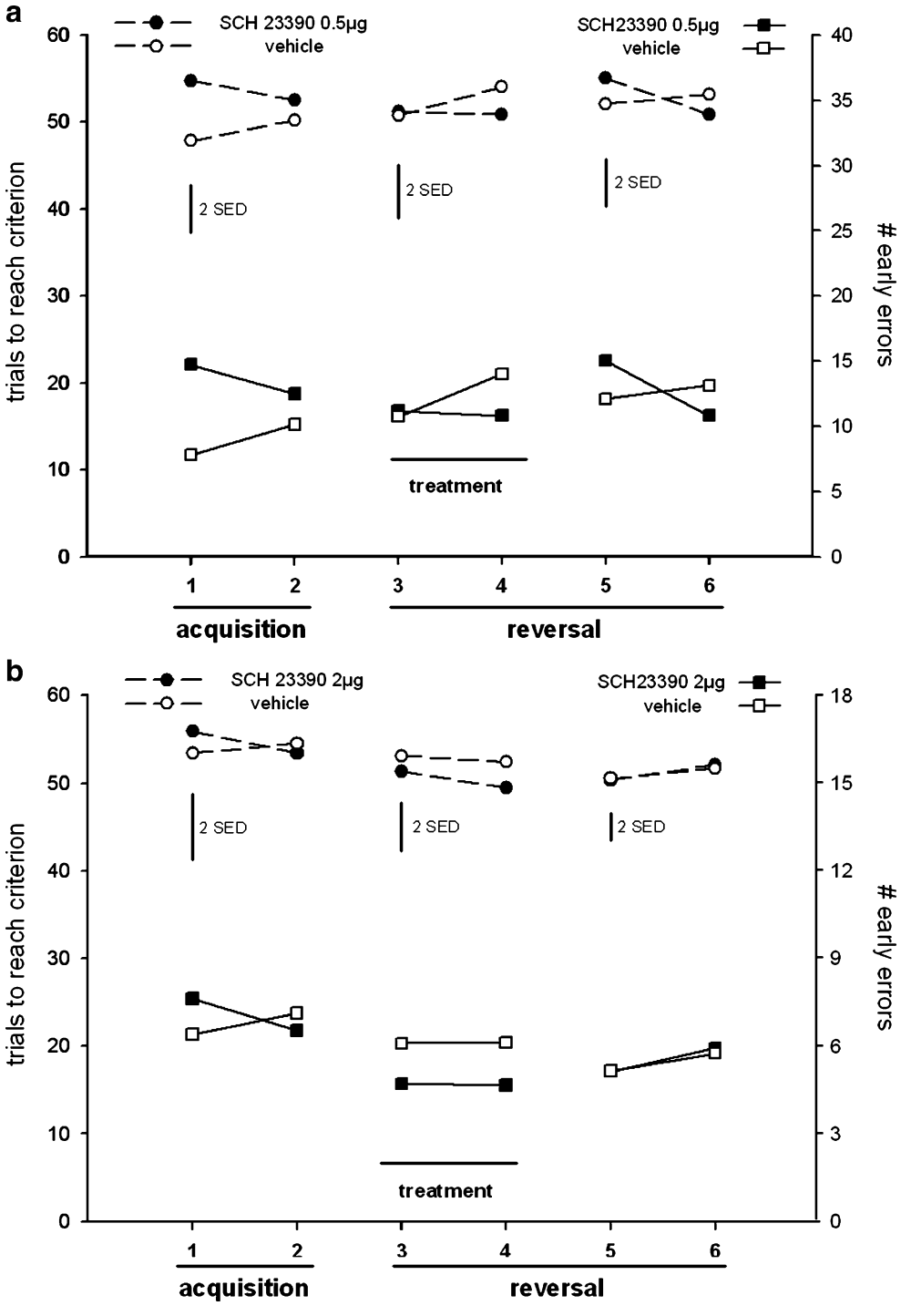

Fig. 5 Effects of intra-AcbC infusion of SCH23390 on the accuracy of responding. Mean trials to reach criterion (40 correct trials; 20 for low and high reward, respectively)(left ordinate) and mean number of early responses (right ordinate) in blocks of three sessions are given; SED bars represents two SEDs of the means (no SEDs were given for early errors). (**a**) 0.5 μg SCH23390 (n=8) or vehicle (n=8) was given on blocks 3–4; infusion of SCH23390 had no significant effects on either variable. (**b**) 2 μg SCH23390 (n=16) or vehicle (n=16) were given on blocks 3–4; infusion of SCH23390 had no significant effects on either variable. Early responses tended to be lower in SCH23390 treated animals on blocks 3–4

Discussion

This study demonstrates that a blockade of D1 or D2 receptors in the AcbC did not inhibit learning a reversal of previously acquired cue–reward magnitude contingencies, but can increase RTs of instrumental responses. In a visual discrimination task as used here, intra-AcbC D1 and D2 receptor-mediated signals seem, therefore, unnecessary to update the reward-predictive significance of cues, rather, they serve to activate instrumental behaviour.

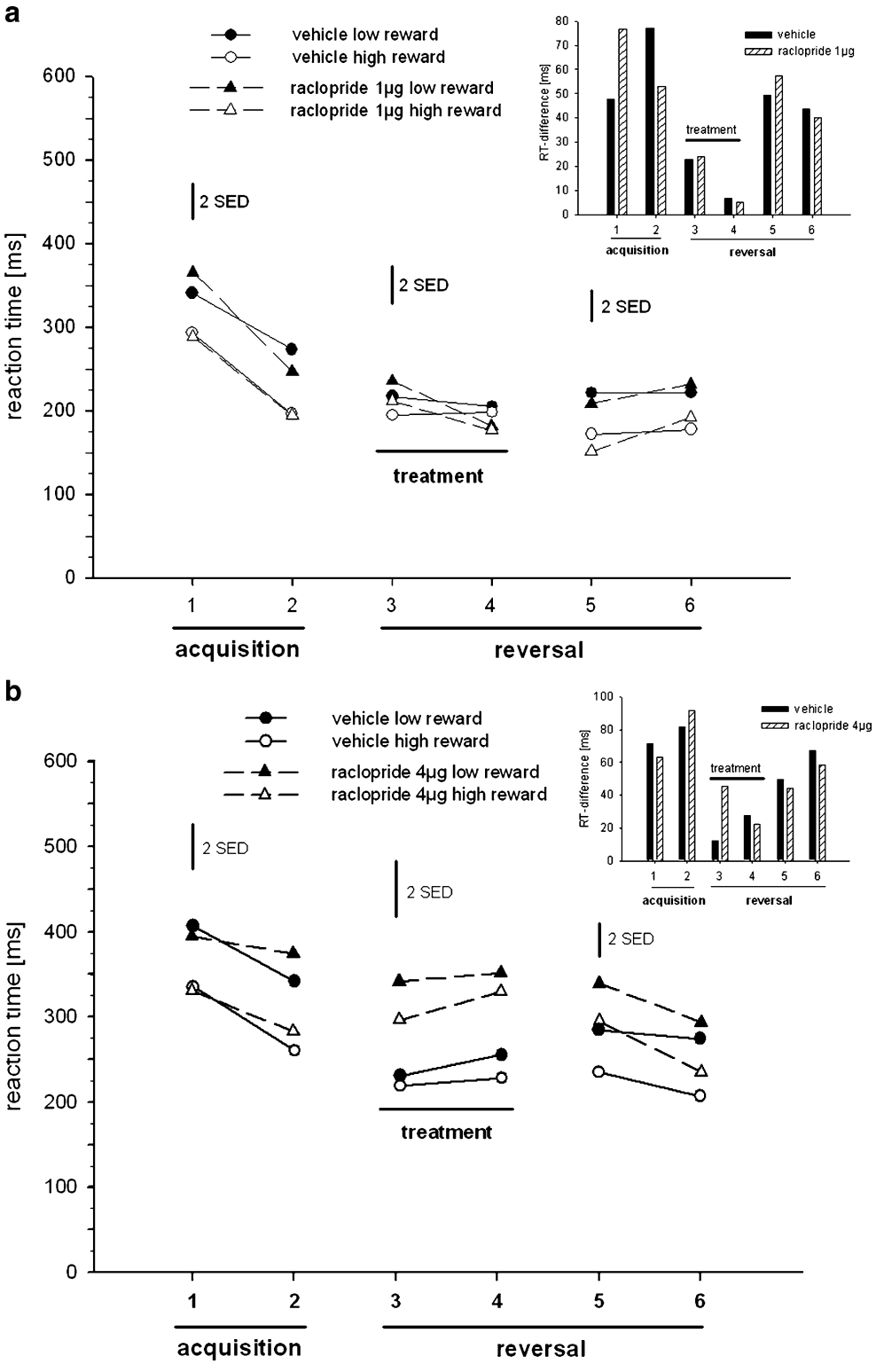

Fig. 6 Effects of intra-AcbC infusion of raclopride. Mean RTs of correct responses in blocks of three sessions are given; SED bars represent two SEDs of the means. Insets: RT differences ($RT_{low\ reward}$ − $RT_{high\ reward}$); i.e. positive values denote faster responding for expected high reward. (**a**) 1 µg raclopride (n=8) or vehicle (n=7) were given on blocks 3–4. RTs were significantly guided by expected reward on blocks 1–2 and 5–6. Infusion of raclopride did not significantly increase RTs on blocks 3–4. (**b**) 4 µg raclopride (n=16) or vehicle (n=15) was given on blocks 3–4. RTs were significantly guided by expected reward on blocks 1–2, 3–4 and 5–6. In addition, infusion of raclopride produced a significant increase in RTs on blocks 3–4

Acquisition of the RT task

In numerous tasks in rats (Brown and Bowman 1995; Hauber et al. 2000), sub-human primates (Hollerman et al. 1998; Kawagoe et al. 1998) and humans (Galvan et al. 2005; O'Doherty et al. 2006), RTs of instrumental responses were related to the expected reward magnitude. In addition, in a number of other settings (Holland and Straub 1979; Sage and Knowlton 2000; Watanabe et al. 2001), response latencies depend on the attractiveness of the outcomes signalled in advance by cues. Likewise, RTs measured here were probably guided by signalled reward

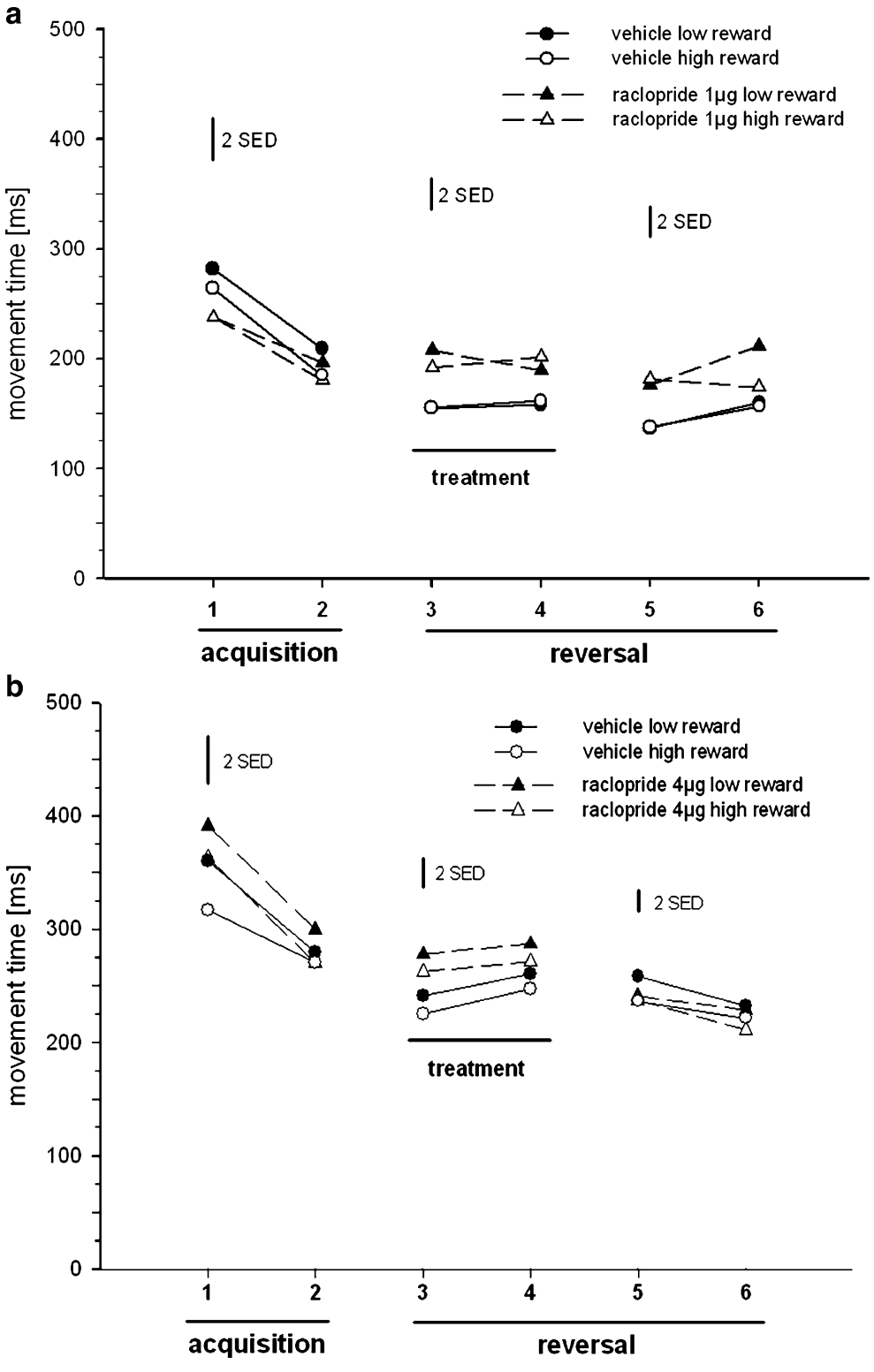

Fig. 7 Effects of intra-AcbC infusion of raclopride. MTs of correct responses in blocks of three sessions are given; SED bars represent two SEDs of the means. (**a**) 1 µg raclopride (n=8) or vehicle (n=7) and (**b**) 4 µg raclopride (n=16) or vehicle (n=15) was given on blocks 3–4. Raclopride did not significantly affect MTs on blocks 3–4

magnitudes and the point in time at which RTs significantly diverge for each reward magnitude might indicate learning of cue-associated reward values. During acquisition, RTs became generally shorter and guided by cue-associated reward magnitudes. In different treatment groups, RTs of responses to expected high vs low reward were about 50–100 ms shorter on the second acquisition block demonstrating rapid discrimination learning as already shown in earlier studies using similar tasks (Brown and Bowman 1995; Giertler et al. 2005).

Likewise, MT became shorter during acquisition. MT is a less appropriate parameter for reward expectancy in rats (Giertler et al. 2003) and primates (Hollerman et al. 1998) and was used here as a sensitive parameter to control for gross drug-induced motor effects (Giertler et al. 2003).

The accuracy of responding measured here was similar to comparable tasks (Brown and Bowman 1995; Hauber

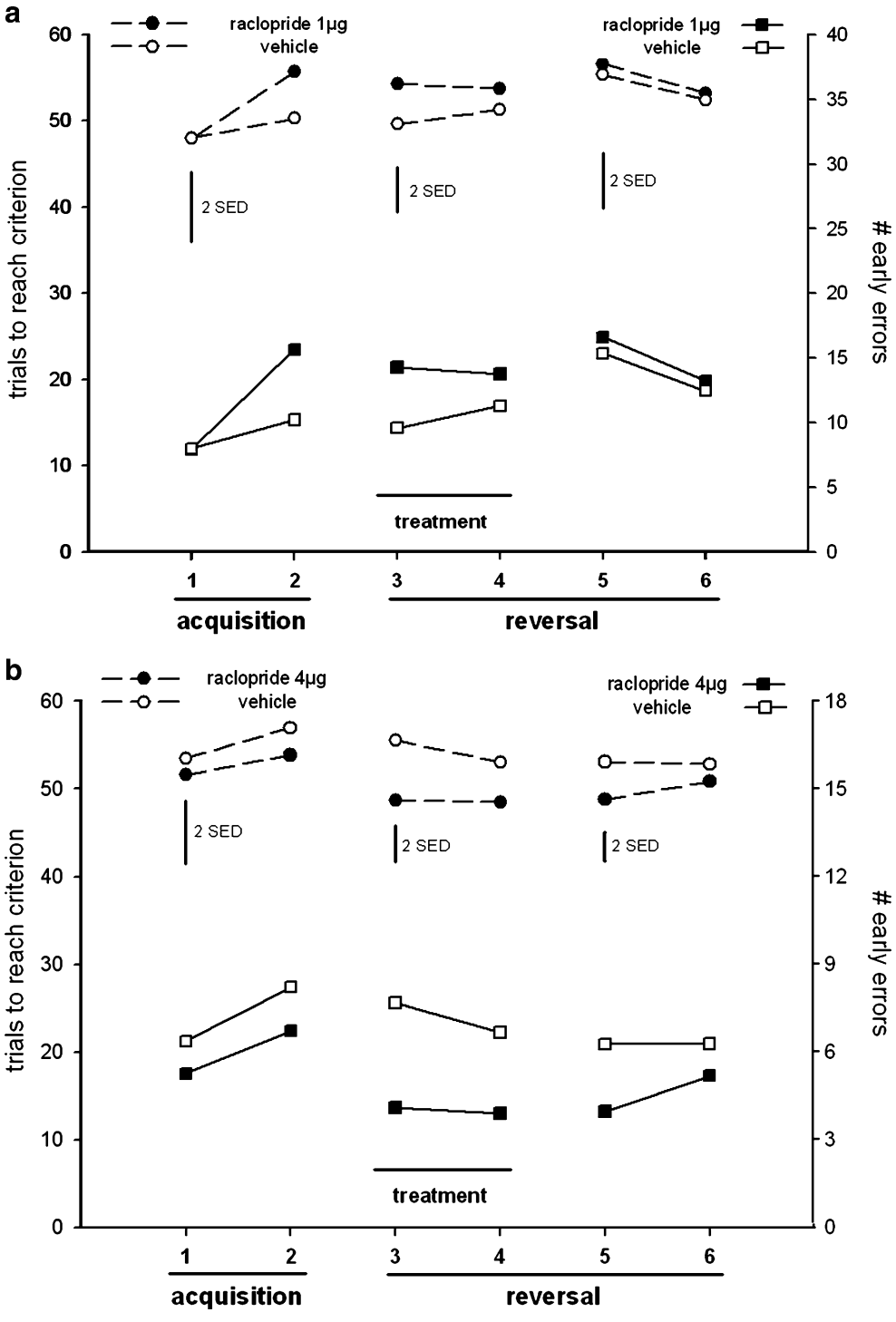

Fig. 8 Effects of intra-AcbC infusion of raclopride on the accuracy of responding. Mean trials to reach criterion (40 correct trials, 20 for low and high reward, respectively)(left ordinate) and mean number of early responses (right ordinate) in blocks of three sessions during acquisition and reversal learning are given. SED bars represent two SEDs of the means (no SEDs were given for early errors). **(a)** 1 µg raclopride (n=8) or vehicle (n=7) was given on blocks 3–4, raclopride had no significant effect on either variable. (**b**) 4 µg raclopride (n=16) or vehicle (n=15) was given on blocks 3–4. Trials to reach criterion and early responses were significantly lower in raclopride treated animals on blocks 3–4

et al. 2000; Laubach et al. 2000) indicating correct learning of the instrumental contingency. Notably, the number of trials to reach criterion often increased during acquisition. This largely reflects the fact that with progressive learning, animals responded faster and made more erroneous early responses, in particular for expected high reward, (Giertler et al. 2005) suggesting that reward magnitude expectation interferes with response preparation.

D1 and D2 receptor blockade did not inhibit discrimination reversal learning

RT differences of responses for expected low and high rewards were used as an index of discriminative learning of current cue-associated reward values. Results indicate discriminative guidance of RTs during reversal learning in SCH23390-treated and vehicle-treated rats as RTs were guided according to the reversed cue–reward magnitude contingencies within a similar number of reversal blocks. This finding suggests that an intra-AcbC D1 receptor blockade did not inhibit reversal learning. Inspection of RT differences indicates that in all treatment groups RTs became shorter for expected high vs low reward on treatment blocks (blocks 3–4) and were significantly guided by reward magnitude on subsequent post-treatment blocks (blocks 5–6). Likewise, raclopride-treated and vehicle-treated animals adapted responding to reversed cue–reward magnitude contingencies within similar number of reversal blocks. In all treatment groups, RTs were shorter for expected high vs low reward on treatment blocks and significantly guided by the expected reward magnitude on post-treatment blocks implying that an AcbC D2 blockade did not affect reversal learning. Accordingly, RT differences became increasingly positive during reversal learning. Some groups, e.g. those treated with a high dose of raclopride and respective vehicle controls already displayed marked reversal learning during blocks 3–4. One variable that accounts for rapid reversal learning seems to be the high proportion of subjects with superior reversal learning capabilities in these groups. A detailed analysis of single sessions from reversal blocks revealed that a great majority of subjects used here can be classified post hoc in high and low performers. High performers displayed rapid reversal learning, i.e. they responded faster to the cue, which now predicts high reward in the first reversal session; low performers in later reversal sessions. Apparently, in groups exhibiting fast reversal learning the proportion of high performers was markedly higher than in other treatment groups, which could account in part for the differences in reversal learning speed (data not shown).

Taken together, our findings suggest that D1 and D2 receptor-mediated signals in the AcbC are not required for reversal learning in an instrumental task as used here.

D1 and D2 receptor blockade slowed responding

Intra-AcbC blockade of D1 and D2 receptors with high drug doses caused a general slowing of responding as indicated by significant increases of RTs and less prominent increases of MTs. These drug-induced changes cannot be easily explained in terms of gross performance deficits. First, SCH23390-induced and raclopride-induced slowing of response execution measured by MTs was moderate. Second, the accuracy of performance was intact in SCH23390-treated and raclopride-treated animals indicating that instrumental contingency was not disrupted by either treatment. Notably, relative to their respective vehicle controls, animals treated with high doses of SCH23390 and raclopride needed fewer trials to reach the criterion number of correct responses. This effect was due to the tendency of drug-treated animals to respond slower and, therefore, to produce fewer early responses.

Previous studies further demonstrated that interference with Acb DA transmission did not substantially reduce primary motivation for natural reward or induce impairments that are caused by gross motor deficits (Salamone et al. 2005). For instance, intra-AcbC infusion of SCH23390 and raclopride in similar doses as used here did not affect locomotor activity, free food consumption or lever pressing under a fixed ratio-1 schedule (Yun et al. 2004a). Likewise, intra-Acb infusions of SCH23390 or raclopride did not alter the temporal characteristics of individual lever presses in an operant task (Nowend et al. 2001). Thus, a gross motor dysfunction or a reduced motivation to eat is unlikely to account for the slowed responding observed here.

Role of accumbens DA in reversal learning and behavioural activation

The involvement of the Acb and its DA input in the multifactorial process of reversal learning is poorly understood. Behavioural studies in rats demonstrated that cell body lesions of the Acb caused reversal learning impairments in spatial tasks (Annett et al. 1989) and some (Ferry et al. 2000), but not all non-spatial (Brown and Bowman 1995) tasks requiring the discrimination of cues predictive of distinct outcomes. Electrophysiological studies using an olfactory go/no go-task that required rats to learn to discriminate two odors, which predicted distinct outcomes revealed that a subset of Acb neurons encoded the cues' learned motivational significance and these neurons reversed their firing selectivity after a reversal of cue–outcome contingencies (Setlow et al. 2003). These and other findings suggest that changes in the neuronal activity of subsets of Acb neurons could assist in adapting existing reward prediction and behaviors to changing environmental conditions (Schultz et al. 2003).

Mesolimbic DA neurons are supposed to play a critical role in these processes. The prediction error hypothesis of DA action assumes that DA signals are necessary to update the predictive significance of cues (Schultz 2006). For instance, if a cue is presented that is normally associated with reward, but reward is withheld, a pause in the tonic firing of DA neurons occurs at the time reward would have been expected. In turn, if a reward exceeds cue-induced expectation, a phasic burst in firing is observed. Such positive ("better than expected") and negative ("worse than expected") prediction error signals are likely to play a crucial role in reversal learning. To our knowledge, there are few studies, if any, investigating the role of AcbC D1 or D2 receptors in learning a reversal of cue–outcome pairings. If DA in the AcbC transmits a prediction error signal that shapes reversal learning, we would expect a pronounced impairment after a DA receptor blockade as, theoretically, the AcbC would have repeatedly received the signal "worse than expected". At variance with this view, our findings indicate that D1 and D2 receptor-mediated signals in AcbC may not be necessary for learning a reversal of cue–reward magnitude contingencies. We cannot exclude that the training during acquisition was not long enough for error prediction mechanisms to be engaged during reversal learning. However, this possibility is less likely because DA cells are capable of signaling negative prediction errors already early during cue–reward learning (Pan et al. 2005). Thus, DA signaling in other DA terminal fields such as the orbitofrontal cortex could play a critical role in this type of reversal learning (see Robbins 2005, for a recent review), particularly because this prefrontal sub-region was found to be important for reversal learning in the task used here (Bohn et al. 2003; Calaminus and Hauber, unpublished observations).

In line with previous evidence (Yun et al. 2004a,b), we observed that intra-Acb D1 and D2 receptor blockade can increase response latencies. These findings support the general notion that the Acb and its DA input amplifies responsiveness to discrete cues predictive of rewarding outcomes (see Cardinal et al. 2002; Salamone et al. 2005, for recent reviews). However, DA depletions or micro-infusion of DA antagonists into the Acb do not always interfere with response latencies; as in some tasks rats were still capable of responding rapidly to reward-predictive cues (Amalric and Koob 1987; Cole and Robbins 1989; Hauber et al. 2000; Robbins 2005) but not in others (Di Ciano and Everitt 2001; Wakabayashi et al. 2004; Yun et al. 2004a,b). The experimental design including task complexity, stimulus predictability or the amount of pre-training varies considerably across these studies and might influence the extent to which intra-AcbC DA antagonism affects response latencies. For instance, contrasting with our present results an intra-Acb blockade of D2 receptors did not impair RT in animals extensively pre-trained on a similar task as used here (Hauber et al. 2000). Furthermore, in some tasks, predictive cues inform animals that reward can be obtained contingent on the performance of a specific behaviour (e.g. Robbins et al. 1990), while in tasks used here, correct identification of reward-predictive cues was not instrumental for correct responding, but served to invigorate responding.

Several DA mediated mechanisms in the AcbC could account for invigorating responses to reward-predictive cues. In instrumental tasks, discriminative cues that predict rewards are an integral component of conditional cue–response–outcome relations (Colwill and Rescorla 1990), but also serve as pavlovian cues (Colwill and Rescorla 1988). Appetitive pavlovian cues can elevate instrumental responding, an effect known as pavlovian to instrumental transfer (PIT) that critically depends on the Acb (Balleine and Killcross 1994; Corbit et al. 2001; de Borchgrave et al. 2002; Hall et al. 2001; Parkinson et al. 2000) and its DA input. For instance, intra-AcbC amphetamine enhanced (Wyvell and Berridge 2000) PIT, while systemic DA receptor blockade (Dickinson et al. 2000) and transient inactivation of the VTA, the origin of the major DA input to the Acb, abolished PIT (Murschall and Hauber 2005). Micro-dialysis studies further revealed that presentation of a pavlovian appetitive cue elevates AcbC DA (Bassareo and Di Chiara 1999; Ito et al. 2000). Likewise, voltammetric analysis demonstrated that reward-predictive cues stimulated Acb DA release on a sub-second scale and that this neurochemical change promoted an instrumental response for reward (Roitman et al. 2004). Furthermore, fMRI studies indicate that the higher VTA activity to a predictive cue, the more the associated food stimulus was preferred (O'Doherty et al. 2006). Thus, reward-predictive cues used here may serve as pavlovian cues, which produce—as a function of the relative attractiveness of the associated outcome—distinct DA-dependent PIT effects. Accordingly, one possibility to explain intact reversal learning but slowed responding is that an intra-AcbC DA receptor antagonism reduced the reward magnitude-specific, excitatory effects of predictive cues on instrumental responding to a similar extent thereby increasing RTs for the expected high and low rewards. Alternatively, cues other than explicit reward magnitude-predictive cues, e.g. cues permanently available in the operant box, might serve as non-specific pavlovian cues, which predict an appetitive outcome thereby speeding RTs of responses both to high and low rewards through AcbC DA mechanisms. If so, the general increase of RTs caused by an intra-AcbC DA D1 and D2 receptor blockade could reflect a reduced invigorating impact of such non-specific pavlovian cues. Interference with Acb DA transmission may not only reduce the vigor of responses to reward-predictive cues. For instance,

Acb DA depletions impaired instrumental performance in ratio schedules, but not in a fixed ratio-1 schedule (Aberman and Salamone 1999; Correa et al. 2002; Ishiwari et al. 2004) and reduced the preference for the high cost–high reward response option when having the choice to obtain a low reward with little effort (e.g. Salamone 1994). Taken together, these and other findings suggest that Acb DA is critically involved in several important activational aspects of reward-directed behavior, e.g. to modulate response speed, vigor and persistence of instrumental behavior (see Salamone et al. 2005 for a review).

In summary, in the visual discrimination task used here, D1 and D2 receptor-mediated signals in the AcbC seem to be unnecessary in updating the reward-predictive significance of cues, rather, these signals serve to activate instrumental responding to reward-predictive cues.

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