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Impairment in a Discrimination Reversal Task After D1 Receptor Blockade in the Pigeon "Prefrontal Cortex"

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Dopamine (DA) is known to modulate cognitive functions of the prefrontal cortex (PFC) of mammals, especially via D1 receptor mechanisms. Like the PFC, the neostriatum caudolaterale (NCL) of birds is characterized by dopaminergic input, and NLC and PFC lesions cause similar deficits. The significance of DA in a color discrimination reversal was assessed by evaluating the effects of bilateral infusions of the D1 receptor antagonist SCH 23390 into the NCL of pigeons (*Columba livia*). Reversal deficits were qualitatively similar to those in mammals. At a low dose, perseveration occurred predominantly to the incorrect stimulus. Higher doses caused additional spatial perseveration. The data demonstrate, for the first time, that D1 receptor mechanisms in the NCL of pigeons contribute substantially to its function in cognitive processes. Thus, the avian NCL and mammalian PFC could represent functionally equivalent neural networks under control of the DA system.

The function of the prefrontal cortex (PFC) in cognitive processes depends on the dopamine (DA) system, which exerts modulatory influence onto PFC neurons through dopaminergic innervation from the ventral tegmental area (VTA; Arnsten, 1998; Goldman-Rakic, 1999). Prefrontal functions have been implicated in different cognitive abilities such as reversal of stimulus–reward associations (Dias, Robbins, & Roberts, 1996; Li & Shao, 1998), inhibitory control (Rolls, Hornak, Wade, & McGrath, 1994), attentional set-shifting (Dias et al., 1996; Owen et al., 1993), decision making (Rogers et al., 1999), and working memory (Bechara, Damasio, Tranel, & Anderson, 1998; Goldman-Rakic, 1996). Dysfunctions of the prefrontal DA system in schizophrenia (Friedman, Temporini, & Davis, 1999; Goldman-Rakic, 1994) or Parkinson's disease (Dubois & Pillon, 1995; Rogers et al., 1998) cause cognitive impairments. Pharmacological treatment of humans with D1 and D2 receptor agonists and antagonists impairs or facilitates performance in specific prefrontal tasks (Luciana, Collins, & Depue, 1998; Mehta, Sahakian, McKenna, & Robbins, 1999; Müller, von Cramon, & Pollmann, 1998). Experimental studies in mammals, including primates, have shown that insufficient as well as excessive DA receptor stimulation is disadvantageous to cognitive functions. A proper and balanced DA turnover is essential for optimal performance (Arnsten, Cai, Murphy, & Goldman-Rakic, 1994; Zahrt, Taylor, Mathew, & Arnsten, 1997). Depletion of DA in the PFC has effects similar to those of PFC lesions (Brozoski, Brown, Rosvold, & Goldman, 1979; Collins, Roberts, Dias, Everitt, & Robbins, 1998). Although different DA receptor subtypes interact and are involved in cognitive functions of the prefrontal system (Arnsten, 1998), much research has focused on the role of D1 receptors. Local injection of D1 receptor antagonists or agonists into the PFC (or treatment with D1 receptor antagonists or agonists) improves or impairs performance in cognitive tasks that tax prefrontal functions; the specific effects often depend on the applied dosage (Cai & Arnsten, 1997; Didriksen, 1995; Granon et al., 2000; Murphy, Arnsten, Goldman-Rakic, & Roth, 1996; Sawaguchi & Goldman-Rakic, 1991, 1994). Electrophysiological studies in vivo and in vitro corroborate the significance of D1 receptor mechanisms for prefrontal functions (Sawaguchi, Matsumura, & Kubota, 1990; Williams & Goldman-Rakic, 1995; Yang & Seamans, 1996).

If specific cognitive functions are critically dependent on the dopaminergic modulation of PFC neurons, one might postulate the same mechanisms to be of importance in nonmammalian neural systems that share common neuroanatomical features with the PFC and subserve similar functions. Comparative neuroanatomical, electrophysiological, and behavioral studies have accumulated evidence suggesting that an area in the avian forebrain, the neostriatum caudolaterale (NCL) is comparable to the mammalian PFC. Both structures share similar patterns of afferents and efferents, such as reciprocal connections with secondary sensory areas of all modalities and projections to somatomotor and limbic areas of the

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basal ganglia (Barbas & Pandya, 1989; Kröner & Güntürkün, 1999; Leutgeb, Husband, Riters, Shimizu, & Bingman, 1996; Metzger, Jiang, & Braun, 1998; Pandya & Yeterian, 1998). Electrophysiological studies have demonstrated that both prefrontal and NCL neurons alter firing rates in response to specific aspects of a behavioral task. Most characteristic of mammalian prefrontal circuits or of functionally equivalent neural networks in birds are reward expectancy neurons and delay units, which are particularly active during the delay period of a working memory task (Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster, 1989; Goldman-Rakic, 1999; Kalt, Diekamp, & Güntürkün, 1999; Watanabe, 1996). In addition, lesions of the avian NCL cause similar deficits as lesions of the mammalian PFC in a number of cognitive tasks sensitive to prefrontal functions. In pigeons, selective lesion deficits occur in reversal learning, go/no-go tasks, delayed alternation, response inhibition and spatial working memory tasks (Aldavert-Vera, Costa-Miserachs, Divac, & Delius, 1999; Gagliardo, Bonadonna, & Divac, 1996; Gagliardo & Divac, 1993; Gagliardo, Mazzoto, & Divac, 1997; Güntürkün, 1997; Hartmann & Güntürkün, 1998; Mogensen & Divac, 1982, 1993). Another important feature of both structures with regard to their role in cognitive functions is the strong dopaminergic input arising from midbrain nuclei of the VTA, which are known to mediate reward contingencies (Björklund, Divac, & Lindvall, 1978; Divac, Björklund, Lindvall, & Passingham, 1978; Divac & Mogensen, 1985; Divac, Mogensen, & Björklund, 1985; Divac, Thibault, Skageberg, Palacios, & Dietl, 1994; Lewis, 1992; Metzger, Jiang, Wang, & Braun, 1997; Waldmann & Güntürkün, 1993; Wynne & Güntürkün, 1995). Specific to both structures is a high density of dopaminergic D1 receptors (Berger, Gaspar, & Verney, 1991; Dietl & Palacios, 1988; Durstewitz, Kröner, Hemmings, & Güntürkün, 1998; Richfield, Young, & Penney, 1987, 1989; Schnabel et al., 1997). In mammals, DA regulates the activity of PFC neurons and cognitive performance primarily via D1 receptors, although other DA receptors might play an additional role (Murphy et al., 1996; Zahrt et al., 1997).

Together, these studies have convincingly demonstrated that the NCL of birds participates in PFC-associated cognitive tasks. In addition, immunohistochemical studies in birds have consistently shown a dopaminergic innervation and, specifically, a dense distribution of D1 receptors in the NCL. It is therefore realistic to assume that in birds, as in mammals, dopaminergic mechanisms are of prime importance for optimal performance in behavioral tasks that tax higher cognitive functions. Similar deficits caused by D1 receptor blockade in the pigeon NCL and mammalian PFC would underline the relevance of DA in nonhomologous but functionally equivalent neural circuits. Furthermore, exploring the parallels of DA actions in prefrontal and prefrontal-like structures, which are embedded in functionally similar circuits but differ distinctly in their fine anatomical structure, might help researchers to better understand the key mechanisms through which DA exerts its modulatory effects. Ultimately, studying cognitive functions in a prefrontal-like structure in pigeons could provide very useful information relevant to the understanding of the neurobiology of mammalian, specifically human, cognition. The present study directly tested the hypothesis that local infusion of a D1 receptor antagonist, SCH 23390, into the NCL of pigeons affects performance in a PFC-mediated reversal task.

It has been suggested that the PFC mediates important aspects of associative learning. Behavioral studies in pigeons have shown that NCL lesions have detrimental effects on reversal learning but not on discrimination performance (Hartmann & Güntürkün, 1998). Reversal tasks have also been used in mammals (Dias et al., 1996; Li & Shao, 1998), including humans (Daum, Schugens, Channon, Polkey, & Gray, 1991; Freedman & Oscar-Berman, 1987; Oscar-Berman & Zola-Morgan, 1980), to assess prefrontal deficits. To master this task, it is necessary to inhibit responses to the previously correct object and to shift attention and motor-set to the previously incorrect object. Thus, a reversal task provides several cognitive measures (i.e., response accuracy, number of perseverative errors, behavioral flexibility) and, in addition, allows for the observation of general motor deficits. Moreover, there is some evidence that the prefrontal DA system is involved in establishing new stimulus–reward contingencies, in signaling errors in the prediction of reward, in maintaining already established stimulus–response associations, and in controlling inhibitory mechanisms during discrimination performance (Richardson & Gratton, 1998; Schultz, 1998; Yamamuro, Hori, Iwano, & Nomura, 1994). The aim of this study was to specifically test the significance of D1 receptor-mediated mechanisms in a discrimination reversal task in pigeons. Reversal performance was tested after extensive training, when the pigeons had reached stable performance levels. Effects of local infusion of saline and different doses of the D1 receptor antagonist SCH 23390 into the avian PFC analogue, the NCL, were investigated in detail by taking different behavioral measures during the reversal task.

Method

Subjects

Subjects were 12 pigeons (*Columba livia*) 1–3 years of age that were obtained from local breeders (registered members of local Pigeon Racing Associations). They were housed in individual cages in a temperature- and humidity-controlled room on a 12-hr light–dark schedule. They were given water and grit ad libitum. One week before the start of test sessions, they were placed on a restricted diet and maintained at 80–85% of their free-feeding weights throughout the experiment. Ten of the 12 pigeons were experimentally naive, and 2 had already participated in a grain–grit discrimination test but had no experience in operant color discrimination tests or reversal learning.

Apparatus

For pretraining and the reversal experiment, a two-key operant chamber (34 × 33 × 36 cm) was used. The chamber was computer-controlled by means of a digital I/O board equipped with electromechanical relays (CIO-PDISO8; Computer Boards, Eichenau, Germany). The conditioning chamber was illuminated by ambient light from a centrally fixed lightbulb. Two operant keys (diameter 2.5 cm) were located on the back wall, 24 cm above the floor and 6 cm from the left and right corners. Each key was transilluminated with either white light during pretraining sessions or red and green light during experimental sessions. The colors were not matched for brightness. A food hopper was located in the center of the back panel, 5 cm above the floor. When raised, it was illuminated by a light fixed above it.

Behavioral Procedure

Pretraining. During pretraining sessions, pigeons were trained to peck reliably on one of two keys, whichever was illuminated with white light.

The position of the illuminated key was randomized within a session and across 10 subsequent sessions (Fellows, 1967). Training sessions consisted of 48 trials with a 5-s intertrial interval. A response to the illuminated key immediately switched off the stimulus light and was rewarded with 3 s of access to food. A single peck on the incorrect key always resulted in a 5-s time-out period during which all lights were turned off, including the lights of the operant keys. The time-out period was immediately followed by the 5-s intertrial interval. No correction trials were inserted. The number of pecks required to trigger reinforcement increased between sessions from one to three (fixed ratio [FR] 1–3). Criterion for advancing from FR1 to FR3 was 80% correct responses in two subsequent sessions. Pretraining continued until the pigeon reached criterion in two successive sessions on an FR3 schedule.

Color discrimination and reversal learning. After the pretraining phase, simultaneous color discrimination and reversal learning began. Each session consisted of 60 trials in which either the red or the green light was reinforced. The two operant keys were illuminated simultaneously, one with red and one with green. The positions of the colors changed randomly within a session and across 10 subsequent sessions, after which the same randomization tables were used again (Fellows, 1967). For half of the subjects, the red key was the positive stimulus in the first session; for the other half, it was the green key. As in pretraining, pigeons were reinforced according to an FR3 schedule with 3 s of access to food and punished with a 5-s time-out after one peck on the incorrect key. All subjects were given one session per day. Learning criterion was 80% correct responses in one session. The values of the two colors were reversed if the pigeon had reached criterion in the previous day's session.

Preoperative color reversal training continued until the pigeon had completed 25 reversals. The number of sessions for each bird to complete 25 such blocks varied greatly and reflected individual learning abilities. Previous experiments have shown that pigeons reach their maximum level of performance after about 20 blocks of reversal learning (Diekamp, Prior, & Güntürkün, 1999; Shimizu & Hodos, 1989). Although individual performance after about 20 reversal blocks varies greatly, learning curves of all subjects were asymptotic and reached a stable level. After completing the reversal training, pigeons were prepared for head surgery, which was required for the infusions.

Surgery

For surgery, pigeons were anesthetized with Ketamine/Rompun (40 mg/kg and 8 mg/kg, respectively, im). Stainless steel guide cannulas (22 gauge; 0.72 mm OD; 11 mm length) were implanted stereotaxically (Karten & Hodos, 1967) and aimed at the pigeons' NCL as currently defined by Waldmann and Güntürkün (1993). To cover the medial to lateral aspect of the NCL, two cannulas were inserted in each side at the following locations: A = 5.25, L = 5.00 and A = 5.25, L = 7.50. Cannulas were inserted with the tip 1 mm below the surface of the brain, secured with dental acrylic, then temporarily closed with a stylet to prevent occlusion. After surgery, pigeons were allowed 2 days for recovery.

Microinfusion and Drugs

Handling and infusion procedures were the same for all postoperative sessions and all subjects. Pigeons were prepared 20 min before the start of each session. They were placed gently in a loose cloth jacket and seated on a foam cushion while the stylets were removed. For infusions of vehicle or SCH 23390, two 12-mm stainless steel infusion cannulas (28 gauge, 0.36 mm OD) extending 1 mm below the guide cannulas were inserted into the two outer guide cannulas. The infusion cannulas were connected by polyethylene tubing to 1-μl Hamilton syringes (Hamilton, Reno, NV) driven by a microdrive infusion pump (PHD2000, Harvard Apparatus, March, Germany). A volume of 0.5 μl saline or 0.5 μl SCH 23390 was injected through each guide cannula into the brain at a speed of 0.25 μl/min. Infusion cannulas remained in place for an additional 3 min to assure optimal diffusion before they were slowly withdrawn. Thereafter, infusions were made through the two inner guide cannulas. Pigeons were tested immediately after completion of the infusion procedure. In postoperative reversal sessions with sham infusions, which were used as control for any stress associated with the procedure, two 8-mm stainless steel pins (rather than injection cannulas) were lowered through the outer guide cannulas. The pins were then connected by perforated polyethylene tubing to the Hamilton syringes. They were left in place for 5 min with the infusion pump running for 2 min. Thereafter, the pins were inserted into the inner guide cannulas according to the same procedure.

All pigeons received three saline infusions (S) and three infusions of the D1 receptor antagonist R(+)-SCH 23390-HCl (D-054; Research Biochemicals International, Natick, MA). The drug was dissolved in distilled water, and aliquots of three different concentrations (0.66 μg/100 μl [C1], 1.00 μg/100 μl [C2] and 1.50 μg/100 μl [C3]) were frozen at −20 °C for later use.

The main actions of the D1 receptor blocker were most likely confined to the NCL and the directly surrounding neostriatum caudale (NC), which also receives dopaminergic afferents and contains a dense distribution of D1 receptors. Radioactively labeled SCH 23390 spreads laterally into the tissue around the infusion site and diffuses about 2 mm at maximum (Granon et al., 2000). In addition, concentrations are dramatically reduced at this distance, even after infusion of much higher doses and larger volumes than those used in the present study. Radioactively labeled glutamate (which of course has different diffusion properties than SCH 23390) infused into the medial neostriatum/hyperstriatum of chicks did not disperse into adjacent areas via the tangent ventricle (Bock, Wolf, & Braun, 1996). On the basis of these studies, it is unlikely that the D1 blocker, which was infused into the NCL of pigeons, also spread far into the medial NC or into the overlaying lateroventral hippocampal complex (cordicoidea dorsolateralis, CDL). No controls were performed for the specificity of the effects of SCH 23390 in the NCL because there is no evidence in the literature thus far that lesions of the CDL or surrounding NC cause deficits in the performance of a preoperatively learned reversal task.

Postoperative Reversal Tests

After surgery, pigeons were initially tested in at least five reversal blocks with sham infusions to adapt them to the procedure and to control for possible effects caused by the surgery or the handling and infusion procedure. The criterion for completing this postoperative, preinfusion training was the completion of five color reversal blocks and, in addition, two color reversals on 2 successive days with at least 80% correct responses.

In subsequent sessions, infusion of the drug (C1–C3) or saline (S) was always followed by three reversal blocks (R) with sham infusions. Both saline and sham infusions served as controls for effects induced by the drug. Infusions were made according to the schedule listed in detail in Figure 2. Infusions of saline or SCH 23390 were always performed in the first session of a new reversal block according to the treatment schedule, whereas sham infusions were performed in all postoperative reversal and nonreversal sessions. As in all training sessions, each reversal block consisted of one to several sessions and lasted until the pigeon met the 80% criterion within a single session. Thus, only during the first session of each reversal block did the bird actually have to reverse the values of the positive and negative stimuli; subsequent nonreversal sessions followed until the bird reached 80% criterion.

Histology and Lesion Reconstruction

Pigeons were injected with heparin (1,000 IU im) 15 min before they were deeply anaesthetized with Equithesin (0.5 ml/100g). They were perfused intracardially with 0.9% saline followed by 4% paraformaldehyde. Their brains were removed, fixed, embedded in gelatin, and sec-

tioned at 40 μm on a freezing microtome. Sections were stained with cresyl violet and used to reconstruct the placements of cannulas. The lowest point of the cannula track was used as estimate for the site of infusion.

Data Analyses and Statistics

Although data were obtained in all sessions, only data recorded during the first session of each reversal block were analyzed; data from nonreversal sessions were disregarded. For each reversal session, several parameters were measured to calculate different behavioral scores.

Response accuracy was calculated as the percentage of correct responses and was used as criterion for starting the next reversal block. The number of trials until the first occurrence of two correct trials and the number of trials the bird needed to complete 10 correct trials in a row were used as an estimate of the flexibility of the bird to shift responses to a new stimulus and to maintain this newly adopted behavior. *Spatial perseveration* was calculated as the percentage of repeated choices to one side, either the left or right pecking key, not counting the first peck in a row of several. It should be noted that the spatial perseveration score is confounded by the given sequence of two colors presented to the left or right side in the present color discrimination and reversal task. In the case of perfect performance or 100% errors and on the basis of the predefined stimulus sequences, pigeons had spatial perseveration scores of 52–54%, because 31–32 stimuli were presented on the same side as the previous one, depending on the particular sequence. (On the other hand, the same spatial perseveration score of about 50% can also be obtained with 50% correct responses.) *Color perseveration* was calculated as the percentage of trials with perseverative errors of choosing the incorrect color. A value of zero would result from flawless performance but also from one-trial error learning (i.e., if the pigeon would correct its error immediately after having chosen the incorrect color). Thus, this value is not necessarily related to overall performance because only perseverative errors were considered.

Effects of treatments (SCH 23390, saline, sham) were analyzed with repeated-measures analysis of variance (ANOVA). For this analysis, means of all behavioral measures were calculated for each block of three reversals with sham infusions, which were interspersed between blocks with SCH 23390 microinfusions, to yield a 12 repeated measures design (df = 11). In addition, to analyze the distribution over the course of the session, perseveration scores were calculated separately for the first, second, and third block of 20 trials with a 3 (Trials 1–20, 21–40, 41–60) × 12 (Treatment) repeated measures ANOVA. The ANOVAs were followed by post hoc comparisons with the one-tailed Tukey's honestly significant difference (HSD) test when appropriate (i.e., when comparing treatment effect to controls); otherwise two-tailed tests were used. Level of significance was set at $p < .05$.

Results

All injection sites were located within the NCL, the region of the pigeon's neostriatum that is characterized by a rich dopaminergic innervation, with one exception. In this case, the guide cannula was positioned in the more ventral part of the neostriatum (see Figure 1). Data from this pigeon were included in the analysis because the three remaining injection sites were correctly located within the target region, so that drug efficacy was unaffected. Lesions produced directly by the insertion of the cannulas were 450–1,000 μm in diameter. There was no major damage due to neuronal loss or gliosis surrounding the cannula track.

Preoperative learning curves for the reversal task reached asymptotic levels of 80% correct responses within a single session after about 20 reversal blocks. Pigeons needed an average of 53.50 (± 5.67) sessions to reach this level (see Figure 2). Compared with the high level of performance during the last five reversals before surgery, during which pigeons performed at a level of 80% (± 3%) correct responses, performance during the five postoperative training sessions dropped only slightly, to 78% (± 3%). This temporary decline in response accuracy was not significant, $t(22) = 0.584$; $p = .565$. Thus, lesions caused by the implantation of guide cannulas, postoperative stress due to extensive handling, or the sham infusion procedure had no adverse effect on behavior. However, to reach the level of preoperative performance, pigeons were trained after surgery until they reached the criterion of 80% correct responses in two subsequent sessions, after which experimental sessions began.

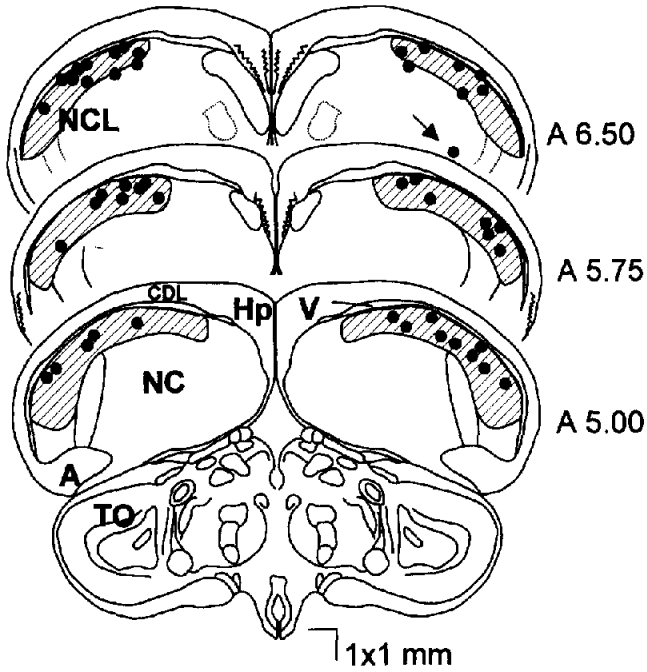

Figure 1. Schematic frontal sections of the pigeon brain illustrating the infusion sites of the injection cannulas. Black dots represent the ventral tips of the cannulas. Drawings of the anterior planes of the pigeon brain (A5.00–A6.50) are taken from the atlas by Karten and Hodos (1967). The target area of the neostriatum caudolaterale (NCL) is obliquely hatched and outlined according to Waldmann and Güntürkün (1993). The arrow points at a misplaced cannula, which was positioned outside the NCL. A = archistriatum; CDL = area corticoidea dorsolateralis; Hp = hippocampus; NC = neostriatum caudale; TO = tectum opticum; V = ventricle.

Performance Scores

The effects of different infusion treatments and control session with sham infusions on cognitive abilities are shown in Figure 3. The ANOVA revealed significant treatment effects on performance, measured as the percentage of correct responses, $F(11, 110) = 7.211$; $p < .0001$. After sham and saline infusions, pigeons mastered reversal sessions at the same high level of performance (> 80% correct) they had reached before surgery after extensive training (see Figure 3A). Administration of the D1 receptor blocker had detrimental effects on response accuracy, which dropped to values of 67%, 69% and 64%, respectively, for the three concentrations of SCH 23390. The decrease in performance

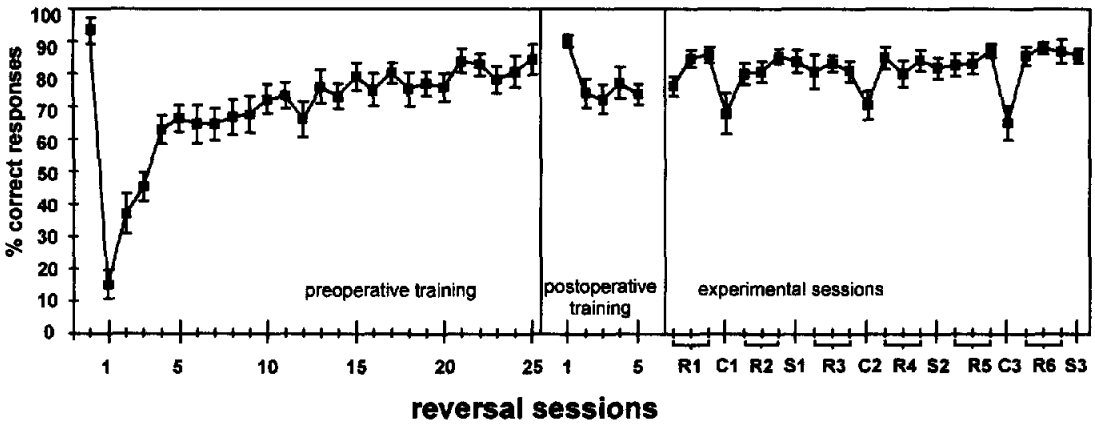

Figure 2. Performance during the first session of each new reversal block shown for 25 preoperative and 5 postoperative training sessions and subsequent test sessions. Bilateral infusions into the neostriatum caudolateral of pigeons were made according to the following schedule: three reversal blocks with sham infusions (R1), 0.66 μg/site of SCH 23390 (C1), three reversal blocks (R2), saline infusion (S1), three reversal blocks (R3), 1.00 μg/site of SCH 23390 (C2), three reversal blocks (R4), saline infusion (S2), three reversal blocks (R5), 1.50 μg/site of SCH 23390 (C3), three reversal blocks (R6), saline infusion (S3). Response criterion for switching the assignment of the colors was 80% correct responses within one session of 60 trials. Not shown are the nonreversal sessions that followed each reversal session if the criterion was not met within a session. Error bars represent *SEM*.

was significant at the lowest and highest doses of SCH 23390 compared with all other reversal sessions after sham and saline infusions ($p < .0001$–$.0179$; Tukey's HSD test, one-tailed). Infusion of SCH 23390 at a dose of 1.00 μg/site resulted in a less pronounced deficit, which was not always significant compared with the performance after saline or sham infusion sessions ($p < .0016$–$.0648$; one-tailed).

During each reversal session, the first occurrence of two hits in succession was highly variable regardless of treatment condition (Figure 3B). Thus, only marginal effects of treatment were found on the number of trials that preceded two successive correct responses, $F(11, 110) = 1.861$; $p = .0523$. In contrast, effects on the more rigid criterion of 10 correct responses in succession were highly significant, $F(11, 110) = 6.838$; $p < .0001$ (Figure 3C). A stable response shift to the new stimulus was observed much later in time (i.e., after many more trials) after D1 receptor blockade than after saline or sham infusions. Pigeons needed, on average, more than 40 trials before they chose the correct response key in 10 consecutive trials after SCH 23390 infusion treatment at a dose of 1.00 μg/site or 1.50 μg/site, significantly more than the average of 23 trials they needed during control sessions ($p < .001$–$.0204$, one-tailed). Thus, degradation in the ability to shift responses was very pronounced at the intermediate and high doses but was not evident at the lowest dose of SCH 23390. This dose had no significant effect on the response shift as compared with control sessions ($p < .0605$–$.2899$; except in comparison to Sessions 1 and 6, $p < .05$).

Perseveration Scores

All pigeons showed distinct perseverative response patterns after D1 receptor blockade (see Figure 4). The ANOVA revealed significant effects of SCH 23390 treatment on color perseveration resulting in consecutive errors, $F(11, 110) = 5.248$; $p < .0001$ (Figure 4A). Post hoc analyses revealed that perseveration of color was strongest after infusion of the lowest dose of SCH 23390 as compared with saline and sham infusions ($p < .0001$–$.0031$, one-tailed). After application of 1.00 μg/site or 1.50 μg/site of SCH 23390, a tendency for color perseveration was only marginally detectable or was not evident as compared with control sessions ($p < .0263$–$.2775$, one-tailed). Infusion of SCH 23390 also affected spatial perseveration, that is, a tendency to choose the same side in the Skinner box and to respond repeatedly on the left or right response keys, $F(11, 110) = 5.784$; $p < .0001$ (Figure 4C). Spatial perseveration scores after infusion of 0.66 μg/site of SCH 23390 did not differ from perseveration scores of control sessions. At the medium SCH 23390 concentration of 1.00 μg/site, pigeons showed a higher tendency for spatial perseveration, which was significantly increased in comparison with all control sessions ($p = .0002$–$.0226$, one-tailed). At the higher drug dose, spatial perseveration scores were significantly increased compared with most of the control sessions ($p = .0005$–$.0922$; one-tailed). Thus, color perseveration was more pronounced at low doses of SCH 23390, whereas spatial perseveration was evident at high doses.

Changes in the tendency to perseverate color over the course of a session were analyzed by calculating separate color perseveration scores for the first, second, and third block of 20 trials within a session (Figure 4B). A 3 (Trial Blocks) × 12 (Treatment) repeated measures ANOVA revealed a significant main effect of trial block, $F(2, 20) = 78.967$; $p < .0001$, a significant treatment effect (see Figure 4A), and a significant Trial Block × Treatment interaction, $F(22, 220) = 2.358$; $p < .0009$. Color perseveration scores were significantly higher during the first 20-trial block as compared with the second or third block ($p < .0002$, two-tailed). In addition, during the first block of trials, perseveration scores were significantly higher after application of the lowest dose of SCH 23390 than after application of the highest dose ($p < .0016$,

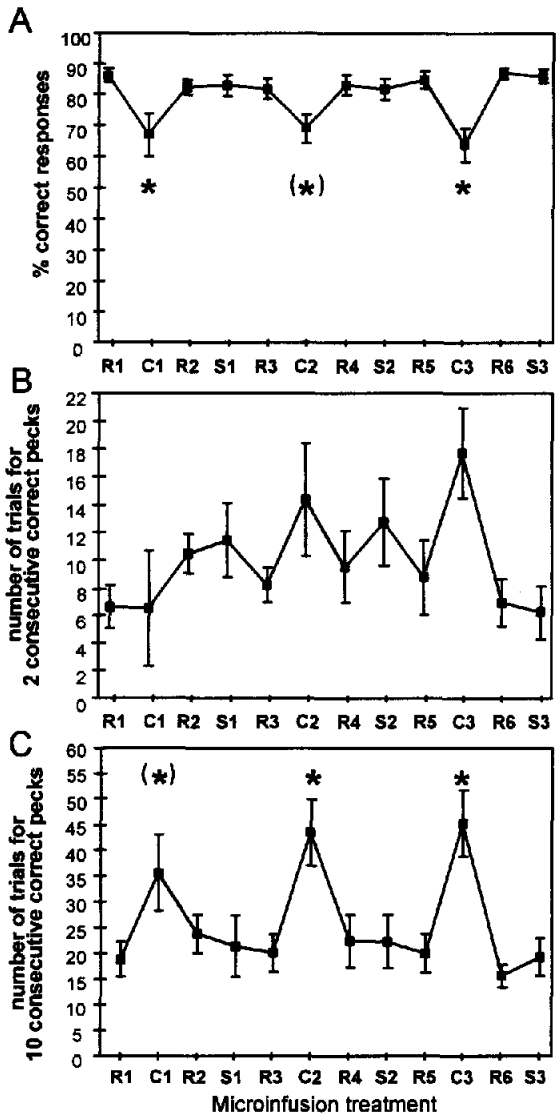

Figure 3. Different performance scores ($M \pm SEM$) in the serial reversal task during reversal sessions after sham infusions (R), saline infusions (S), and infusions of different doses of SCH 23390 (C1–C3) into the neostriatum caudolaterale. A: Percentage of correct responses during reversal sessions. Effects of infusion treatments were found to be significant. B: Number of trials until the first occurrence of two correct responses in two consecutive trials. C: Number of trials before responding correctly in 10 consecutive trials. Significant deficits were found in blocks after drug infusions. Asterisks indicate significant effects of the drug treatment compared with all other control sessions (sham and saline infusion treatments) as a result of a repeated measures analysis of variance followed by post hoc comparisons with one-tailed Tukey's honestly significant difference test ($p < .05$). Asterisks in brackets indicate that most, but not all, post hoc tests against the performance in control sessions were significant.

two-tailed) or after control and saline sessions ($p < .0002$–$.040$, one-tailed). In contrast, the medium and higher concentrations did not raise perseveration scores above the level of control sessions during the first 20 trials of a session. The effects of the D1 blockade were also evident during later parts of a session. During the second and third block of trials, perseveration scores still appeared to be slightly elevated after D1 blockade, independent of the applied dose, as compared to control sessions. But only the lowest dose caused a higher number of perseveration errors during the third block of trials as compared to all the control sessions ($p < .0084$; one-tailed). In general, however, elevated perseveration scores due to D1 blockade during the second and third block of trials were in the range of perseveration scores from control sessions during the first block of trials.

Spatial perseveration scores also changed in the course of a session (Figure 4D). A 3 × 12 repeated measures ANOVA yielded a significant main effect of trial block, $F(2, 20) = 34.609$; $p < .0001$, and a significant treatment effect (see Figure 4B), but no significant Trial Block × Treatment interaction, $F(22, 220) = 0.512$; $p > .9671$. Perseveration scores were significantly higher during the first block of trials as compared to the second and third blocks ($p < .0002$, two-tailed Tukey's HSD test). Although medium and high doses of SCH 23390 had a strong impact on spatial perseveration tendencies at the beginning of a session, with perseveration scores of 77% (± 4%) and 79% (± 10%), respectively, these values were not significantly higher than the perseveration scores during control sessions.

Discussion

To our knowledge, this is the first study demonstrating that microinfusion of the D1 receptor antagonist SCH 23390 into the NCL of pigeons has a distinct effect on a visual discrimination reversal, a task that is commonly used to assess cognitive functions of the PFC. The results show that DA-related deficits in pigeons are characterized by reduced performance scores and perseverative response habits, and thus are quantitatively and qualitatively similar to impairments of mammals with frontal lesions or frontal DA depletion. In this respect, the present data confirm the long-held notion that DA is of importance for proper function of this particular association area in the avian forebrain, as much as the prefrontal DA system is involved in a number of cognitive processes in mammals.

Deficits in Performance

In pigeons, performance levels in the reversal task dropped significantly after local D1 receptor blockade in the PFC-like NCL, whereas local application of saline had no effect. These deficits are similar to those that have been observed in a visual pattern reversal after NCL lesions in pigeons (Hartmann & Güntürkün, 1998), and in spatial and object discrimination reversals after prefrontal lesions in mammals (rats: Granon, Vidal, Thinus-Blanc, Changeux, & Poucet, 1994; Kolb, Nonneman, & Singh, 1974; Li & Shao, 1998; monkeys: Dias et al., 1996; Meunier, Bachevalier, & Mishkin, 1997; Oscar-Berman, 1978; humans: Daum et al., 1991; Verin et al., 1993).

Results of the D1 receptor blockade in pigeons are even more compelling with respect to prefrontal-like functions of the NCL, when comparing the effects to prefrontal DA-related deficits in mammals. Lowered catecholamine levels due to age or DA dysfunctions cause characteristic cognitive deficits in humans and other primates (Arnsten, 1998; Arnsten et al., 1994; Dubois &

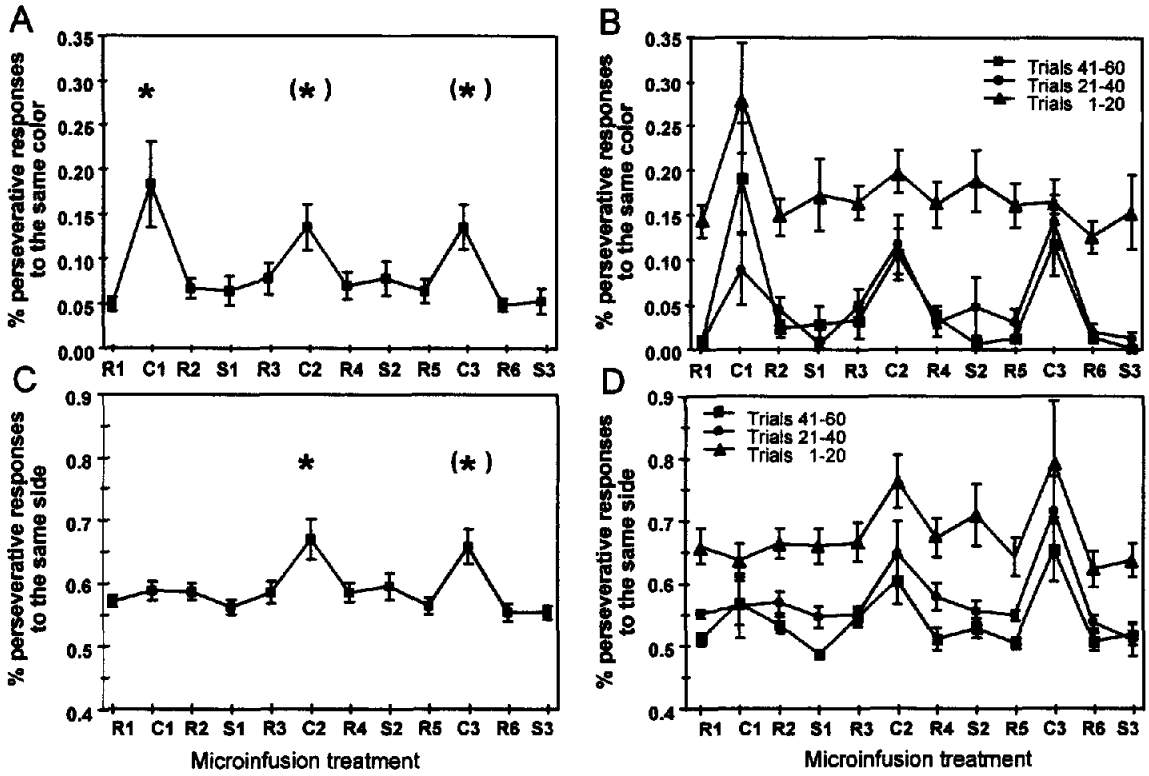

Figure 4. Perseveration scores ($M \pm SEM$) in the reversal task during sessions after sham infusions (R), saline infusions (S), and infusions of different doses of SCH 23390 (C1–C3) into the neostriatum caudolaterale. A: Perseveration of color, measured as the tendency to perseverate responses to the incorrect color across trials. A significant increase in perseverative response patterns was found only at the lowest dose. B: Color perseveration values separated for the first, second, and third block of 20 trials within a session. C: Spatial perseveration, measured as the percentage of repeated responses to the same side regardless of performance. A drug-induced significant increase in perseverative response patterns was found at medium and high drug doses. D: Spatial perseveration values separated for the first, second, and third block of 20 trials within a session. Asterisks indicate significant effects of the drug treatment compared with all other control sessions (sham and saline infusion treatments) as a result of a repeated measures analysis of variance followed by post hoc comparisons with one-tailed Tukey's honestly significant difference test ($p < .05$). Asterisks in brackets indicate that most, but not all, post hoc tests against the performance in control sessions were significant.

Pillon, 1995; Freedman & Oscar-Berman, 1989; Goldman-Rakic, 1994). In rats and monkeys, impaired performance has been found after prefrontal catecholamine depletion through 6-OHDA lesions (Brozoski et al., 1979; Bubser & Schmidt, 1990; Collins et al., 1998; Roberts et al., 1994), as well as after local injection of different selective or nonselective D1 receptor antagonists (Broersen, Heinsbroek, de Bruin, Uylings, & Olivier, 1995; Izquierdo et al., 1998; Sawaguchi & Goldman-Rakic, 1991, 1994). Recent studies emphasize the modulatory action of DA on the performance in working memory tasks, as insufficient as well as excessive D1 receptor stimulation in the PFC is detrimental (Arnsten, 1998; Murphy et al., 1996; Zahrt et al., 1997). Dose-related improvements have been reported after D1 receptor agonist treatment in aged monkeys (Cai & Arnsten, 1997). Dose-related impairments have been found after infusion of SCH 23390 (Broersen et al., 1995; Sawaguchi & Goldman-Rakic, 1991, 1994), with higher doses of the D1 receptor antagonist producing larger error scores. Prefrontal DA transmission has also been found to be relevant in discriminative behavior, in which DA is essential for establishing and updating stimulus–reward associations (Bassareo & Di Chiara, 1997; Richardson & Gratton, 1998; Schultz, 1998; Yamamuro et al., 1994).

The data of this study demonstrate that blockade of D1 receptors is detrimental to the performance in discrimination reversal, which is consistent with the idea that DA-dependent learning is mediated by activation of D1 receptors that facilitate the glutamatergic neurotransmission at NMDA receptors (Schultz, 1998). Infusion of the highest dose of SCH 23390 into the NCL of pigeons also resulted in slightly higher error scores in the reversal task than did infusions of the lowest and medium dose. The fact that impairments in pigeons were not as prominently dose-dependent as those seen in monkeys or rats might be attributed to the narrow range of SCH 23390 doses infused into the pigeons' NCL. In other studies, the amount of SCH 23390 tested was increased by a factor of up to 6 from the lowest to highest dose (e.g., Broersen et al., 1995: 0.2–1.0 μg/side in rats), whereas in this study, the increase was

only 2.3-fold, with a significant drop in performance accuracy already seen at the lowest dose of 0.66 μg/site. Therefore, infusions of a broader range of doses of SCH 23390 into the NCL of pigeons presumably would lead to more obvious dose-dependent performance deficits as observed in mammals.

Qualitative Characteristics of Impairments

Detailed analyses of the deficits in the reversal task after D1 receptor blockade in pigeons revealed qualitative impairments, which are characteristic of prefrontal damage. Reversal learning involves different cognitive processes, which are related to processing of inhibitory control, interference of past and present experience, and the ability to shift attention to a new stimulus (Dias et al., 1996; Shimizu & Hodos, 1989). Disruption of DA mechanisms in the prefrontal-like NCL might affect each one of these in a differential manner.

Prefrontal damage affects shifting and maintaining attention to a known, previously unrewarded stimulus but not to a novel stimulus (Dias et al., 1996; Owen, Roberts, Polkey, Sahakian, & Robbins, 1991). Typically, the number of trials before the first occurrence of two consecutive correct responses in a reversal task is not different between controls and subjects with prefrontal lesions (Dias et al., 1996), or after D1 receptor blockade in prefrontal areas, as investigated in this study. The first correct response in a reversal might represent a fortuitous event rather than an active switch to the new stimulus. In contrast, the number of trials needed before a larger number of consecutive correct responses is emitted is dramatically increased in humans, monkeys, or rats with damage to prefrontal functions (Dias et al., 1996; Li & Shao, 1998; Owen et al., 1993). Similar dose-dependent deficits in the ability to shift behavioral set within the same perceptual dimension (color) was found in pigeons after D1 receptor blockade in the NCL.

This deficit in set-shifting can be linked to a failure to shift attention away from the previously rewarded stimulus or to a failure to focus attention on the new stimulus (Owen et al., 1993). The former is evident in a tendency to perseverate responses according to the old stimulus–response or stimulus–reward contingencies, and it is characteristic for subjects with frontal damage. The latter can be described as an inability to respond to a previously irrelevant stimulus and is known from deficits involving the basal ganglia or temporal lobe (Jones & Mishkin, 1972; Owen et al., 1993). In accordance with these observations, perseveration errors have been reported in numerous studies investigating prefrontal functions (Dias et al., 1996; Freedman, Black, Ebert, & Binns, 1998; Granon et al., 1994; Iversen & Mishkin, 1970; Oscar-Berman, 1978; Owen et al., 1993).

Perseveration was also the major deficit in the present study in pigeons after D1 receptor blockade in the NCL. With regard to color as the relevant stimulus category, pigeons perseverated most after infusion of the lowest dose of SCH 23390. Independent of their performance in reversals, pigeons also showed response perseveration in their choice of the pecking key (i.e., perseveration of response side), which, in contrast to color perseveration, only emerged after application of medium to high doses of SCH 23390. These perseveration patterns suggest that a low dose of SCH 23390 affects only color perseveration, leaving the animals still able to switch sides. Higher doses of SCH 23390, in addition, influence the ability to spatially switch between two response keys. This pattern compares well with that seen after prefrontal lesions in marmosets. Dias et al. (1996) report that impairments in visual discrimination reversal in prefrontal marmosets were mainly due to the subjects staying fixated in a certain position in front of the hidden reward during a delay task. Thus, it is conceivable that a severe breakdown of prefrontal processing after complete D1 blockade or extensive lesions increases disinhibition to the extent that subjects are unable to switch to another response position.

Anatomical Considerations

Although we are aware of the fact that different subregions of the PFC in mammals are characterized by subtle anatomical and functional differences (Rushworth & Owen, 1998), we did not comment on these subdivisions with regard to possible similarities in the pigeon forebrain for several reasons. There is no agreement on how, or to what extent, subdivisions of the mammalian PFC are related to a functional differentiation. Behavioral deficits observed after lesions of distinct subdivisions of the PFC and after parietal, temporal, or hippocampal lesions are often similar, so that functional distinctions between these areas based on a single behavioral task are often not possible. Moreover, homologies regarding the PFC are difficult to establish, even between primates and other mammals (Preuss, 1995). The nucleus mediodorsalis (MD), which is the main source of thalamic input to the PFC, is commonly used to define the PFC in mammals (Akert, 1964; Preuss, 1995). In pigeons, thalamic input is provided by the nucleus dorsolateralis posterior thalami, which is not homologous to the MD (Güntürkün, 1997; Metzger et al., 1997; Veenman, Medina, & Reiner, 1997). Despite this difference in the thalamic afferents, the avian NCL is believed to be a functional equivalent to the mammalian PFC, on the basis of similarities in connectivity with other structures (Barbas & Pandya, 1989; Kröner & Güntürkün, 1999; Leutgeb et al., 1996; Pandya & Yeterian, 1998), neurotransmitter composition (Berger et al., 1991; Björklund et al. 1978; Dietl & Palacios, 1988; Divac et al. 1978, 1994; Divac & Mogensen, 1985; Durstewitz et al., 1998; Lewis, 1992; Metzger et al., 1997; Richfield et al., 1987, 1989; Schnabel et al., 1997; Waldmann & Güntürkün, 1993; Wynne & Güntürkün, 1995), behavioral evidence (Gagliardo et al., 1996; Gagliardo, Mazzotto, & Divac, 1997; Güntürkün, 1997; Hartmann & Güntürkün, 1998; Mogensen & Divac, 1982, 1993), and similar electrophysiological characteristics of neurons (Funahashi et al., 1989; Fuster, 1989; Goldman-Rakic, 1999; Kalt et al., 1999; Watanabe, 1996). More recently, subdivisions of the NCL have been described on the basis of distinct in- and output patterns (Kröner & Güntürkün, 1999) and on differential immunoreactivity to different substances (Riters, Erichsen, Krebs, & Bingman, 1999). However, it is not clear whether these subdivisions in the pigeons' NCL are related to prefrontal subdivisions of mammals.

Summary

Results of the present study demonstrate that the dopaminergic system of the NCL in pigeons plays an important role in discrimination reversal. Because D1 receptor blockade in the NCL of pigeons severely disrupts performance in the reversal task, and because deficits are qualitatively similar to those seen after prefrontal damage or interference with frontal DA functions, parallels

between the mammalian and avian brain structure can be extended. These studies therefore demonstrate that DA-dependent, modulatory mechanisms of the PFC or PFC analogues are essential to restructuring learned behavioral strategies according to new stimulus–reward contingencies.

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