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Impaired Learning of a Color Reversal Task After NMDA Receptor Blockade in the Pigeon (*Columba livia*) Associative Forebrain (Neostriatum Caudolaterale)

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The neostriatum caudolaterale (NCL) in the pigeon (*Columba livia*) forebrain is a multisensory associative area and a functional equivalent to the mammalian prefrontal cortex (PFC). To investigate the role of *N*-methyl-D-aspartate (NMDA) receptors in the NCL for learning flexibility, the authors trained pigeons in a color reversal task while locally blocking NMDA receptors with D,L-2-2-amino-5-phosphonovalerate (AP-5). Controls received saline injections. AP-5-treated pigeons made significantly more errors and showed significantly stronger perseveration in a learning strategy applied by both groups but were unimpaired in initial learning. Results indicate that NMDA receptors in the NCL are necessary for efficient performance in this PFC-sensitive task, and that they are involved in extinction of obsolete information rather than in acquiring new information.

The aim of the present study was to examine the role of *N*-methyl-D-aspartate (NMDA) receptors in the neostriatum caudolaterale (NCL) of the pigeon in a task sensitive for prefrontal functions. A large body of evidence suggests the NCL to be a functional equivalent to the mammalian prefrontal cortex (PFC); this was first pointed out by Divac, who coined the term posterodorso-lateral neostriatum to describe this brain area (Mogensen & Divac, 1982). Comparable to the PFC, the NCL maintains reciprocal connections to secondary sensory areas of all modalities and projections to somatomotor and limbic zones (Kröner & Güntürkün, 1999; Leutgeb, Husband, Riters, Shimizu, & Bingman, 1996; Metzger, Jiang, & Braun, 1998; Pandya & Yeterian, 1996). Furthermore, it receives a dense dopaminergic innervation from midbrain structures (Divac, Thibault, Skageberg, Palacios, & Dietl, 1994; Metzger et al., 1998; Waldmann & Güntürkün, 1993; Wynne & Güntürkün, 1995). Behavioral evidence shows that lesions of the NCL lead to performance deficits in working memory tasks (Gagliardo, Bonadonna, & Divac, 1996; Gagliardo, Mazzotto, & Divac, 1997; Güntürkün, 1997; Mogensen & Divac, 1982, 1993), pattern reversal (Hartmann & Güntürkün, 1998), delayed alternation (Gagliardo & Divac, 1993), and go/no-go-tasks (Aldavert-Vera, Costa-Miserachs, Divac, & Delius, 1999; Güntürkün, 1997). Moreover, temporary blockade of dopamine D_1 receptors in the NCL has been found to cause impairments in a discrimination reversal task (Diekamp, Kalt, Ruhm, Koch, & Güntürkün, 2001) and a working memory task (Güntürkün & Durstewitz, 2000). Electrophysiological studies identified NCL neurons in that—comparable to PFC neurons—show delay- and reward expectancy-related activity (Fuster, 1989; Kalt, Diekamp, & Güntürkün, 1999; Watanabe, 1996). Thus, multiple evidence points to a functional equivalency between the avian NCL and the mammalian PFC. High densities of NMDA receptors have been identified within the avian NCL, and it is conceivable that they play a prominent role in some aspects of functions subserved by the NCL. Indeed, NMDA receptors in the NCL of young chickens have been shown to be involved in one-trial passive-avoidance learning (Stewart, Bourne, & Steele, 1992) and imprinting (Bock, Schnabel, & Braun, 1997; Bock, Wolf, & Braun, 1996). These learning processes are characterized by their rapid onset and, once established, by their long-lasting stability. However, because high densities of NMDA receptors also occur in adult pigeons, it is likely that they also play a role in other learning functions.

Reversal learning is a typical task that probes behavioral flexibility, a feature attributed to the PFC. In a reversal task, animals or human subjects have to learn that the previously rewarded stimulus (S+) is now incorrect, and that the former S− is the new S+. Lesions to the PFC drastically impair performance in reversal tasks (Daum, Schugens, Channon, Polkey, & Gray, 1991; Rosenkilde, 1979). To our knowledge, no study has ever analyzed whether prefrontal NMDA receptors mediate the ability for reversal learning. Therefore, the first aim of the present study was to investigate whether these receptors within the NCL are involved in reversal learning. A detailed analysis of the reversal learning process shows that subjects have to acquire two different sets of information: first, learning to cease responding to the former S+, and second, learning that the previous S− has to be selected (Macphail, 1976). Given the differential ability of NMDA receptors to modulate long-term depression (LTD) and long-term potentiation (LTP; Castro-Alamancos, Donoghue, & Connors, 1995; Gean & Lin, 1993; Hrabetova & Sacktor, 1997), the second aim of the present study was to establish a detailed behavioral analysis to reveal the specific role of these receptors in a "frontal" area, in a task probing behavioral flexibility.

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Method

Subjects

Subjects were 15 unsexed and experimentally naive pigeons (*Columba livia*), age 1–7 years, obtained from local breeders. They were individually housed in cages in a temperature- and humidity-controlled room on a 12-hr light–dark schedule. During experiments, they were maintained at 80% of their free-feeding weight and received water and grit ad libitum.

Apparatus

Two conventional and functionally identical Skinner boxes (36 cm long × 34 cm high × 36 cm wide) were used. Each was equipped with two pecking keys and a solenoid-operated food hopper in the back wall and was computer-controlled by means of a digital input/output board. On the pecking keys (2.5 cm in diameter), white light was displayed for pretraining, and red or green light was displayed for experimental sessions. The food hopper was situated in the center of the wall, below the two keys. Above the food hopper, a reinforcement light signaled the availability of food. The Skinner box was illuminated by a houselight.

Pretraining

The pigeons first received an autoshaping procedure in which they acquired the association between responding to a single pecking key illuminated by white light and subsequent food reward. This was followed by pretraining, during which pigeons learned to discriminate between two pecking keys and to respond only to the key displaying white light. Pretraining lasted until pigeons reached learning criterion (at least 80% correct responses in each of three consecutive sessions).

Surgery

For surgery, pigeons were anesthetized with Ketamine–Rompun (40 mg/kg and 8 mg/kg, respectively, im). Stainless steel guide cannulas were implanted stereotaxically (Karten & Hodos, 1967), aiming at the NCL. Two cannulas per hemisphere were vertically inserted to reach the following coordinates: A 5.25, L 5.00; and A 5.25, L 7.50. Cannulas were inserted to 1 mm below the brain surface and were secured with dental acrylic. After 3–4 days of recovery, pigeons were tested for retention of the pretraining task (criterion: 80% correct responses in the retention session).

Color Reversal Learning Procedure

Experimental training consisted of seven sessions: the first one for the acquisition of a color discrimination (red vs. green), and six subsequent sessions for color reversal learning. Each of the seven sessions was followed by a retention session approximately 2 days later. The interval between the retention session and the next reversal session was about 24 hr. All acquisition, reversal, and retention sessions lasted until learning criterion (15 correct responses in a row) was reached, with session duration not to exceed 3 hr.

In the acquisition session, the color that the pigeon chose first was considered the S+ (positive stimulus) for the session. In each of the following color reversal sessions, the contingencies of the colors were reversed: If in acquisition the S+ was red, in Reversal 1 it was green, in Reversal 2 it was red again, and so on. The stimulus colors were displayed on the pecking keys according to a quasirandomized sequence (Fellows, 1967). We applied a fixed ratio-3 schedule, allowing 3 s access to food after a correct response and delivering a 5-s time-out after a response to the incorrect color.

Immediately before the acquisition and reversal sessions, experimental pigeons received infusions of the competitive NMDA receptor antagonist D,L-2-2-amino-5-phosphonovalerate (AP-5) locally into the NCL (AP-5 dissolved in saline solution; total volume = 2 μl, containing 10 μg AP-5, 0.5 μl [2.5 μg AP-5] per cannula). Infusions were made through interior cannulas protruding 1 mm from the tip of the implanted cannulas that guided them into the brain tissue. We used a microinfusion pump equipped with two 1-μl Hamilton (Reno, NV) syringes to deliver the volume at a flow rate of 0.2 μl/min. Afterward, the infusion cannulas remained in place for another 2 min to allow for diffusion of the infused volume. To infuse through all four cannulas, we performed this procedure twice. Control pigeons were submitted to the same procedure, receiving saline solution only. Immediately after the infusion procedure, which took about 12–15 min, the pigeons had to perform the task. All pigeons received a total of seven infusions of either AP-5 or vehicle.

Histology

To reconstruct the locations of the guide cannulas, we perfused the pigeons intracardially with 0.9% (wt/vol) saline (40 °C) and a 4% (wt/vol) paraformaldehyde solution (4 °C). The brains were removed, postfixed, and cut into 40-μm frontal slices on a freezing microtome. The slices were stained with cresyl violet. The lowest point of the lesion left by the cannulas was considered the injection site.

Results

All injection sites were located within the NCL. Seventy-eight percent of the sites were located within a range of ±0.5 mm from A 5.25. Twenty-two percent were situated anteriorly up to A 6.25 (see Figure 1).

During training sessions, the total number of errors and percentage of errors were recorded for each session for each pigeon. The color acquisition performance of the AP-5 ($n = 7$) and saline ($n = 8$) groups was compared by means of a one-factor analysis of variance (ANOVA, one-tailed). The color reversal performance of AP-5 and saline groups was compared by means of a 2 (groups) × 6 (sessions) repeated measures ANOVA (one-tailed) for all of the above scores. The tests for total number of errors and percentage of errors were one-tailed due to our directed hypothesis: Considering the role of NMDA receptors for various learning phenomena, we expected the AP-5 group to show poorer performance, as revealed by a larger number of errors. Additional tests examining the learning strategies were two-tailed.

In the acquisition of the color discrimination, there were no significant differences in the total number of errors between groups (see Figure 2 and Figure 3).

In color reversal learning, the AP-5 group made more errors than controls until reaching criterion. This difference was significant for the absolute number of errors, $F(1) = 5.94$, $p < .05$ (one-tailed), as well as for relative error rates, $F(1) = 7.02$, $p < .01$ (one-tailed). There was a significant effect of the sequence of reversal sessions, both for absolute errors, $F(5) = 19.92$, $p < .01$, and for relative errors, $F(5) = 25.49$, $p < .01$. No significant interactions were found in either total errors or percentage of errors. In both groups, error rates were lower in later reversal sessions (see Figure 3 and Figure 4).

The pigeons' behavior during a reversal session could be compartmentalized into distinct types that might represent the use of diverse strategies to solve the task. These were first described by Macphail (1976), who distinguished between three successive measures: color perseveration, side perseveration, and correct strategy. *Color perseveration* represents the number of trials in which the subject responds continuously to the wrong color despite negative feedback. *Side perseveration* is a measure for those trials in which the subject responds to one pecking key only, irrespective

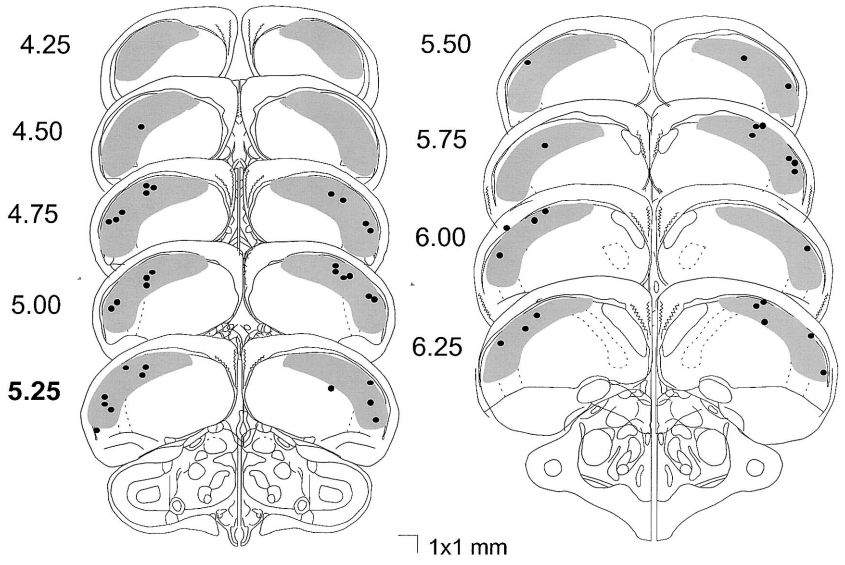

Figure 1. Schematic frontal sections of the pigeon brain showing the injection sites for the AP-5 and/or saline solutions. Dots represent the lower tips of the cannulas; numbers represent the distance (in millimeters) anterior to the center of the ear bars; and boldface indicates the frontal plane level at which injections were aimed. The neostriatum caudolaterale area according to Waldmann and Güntürkün (1993) is depicted in light gray. From *Stereotaxic Atlas of the Brain of the Pigeon (Columba livia)*, by H. J. Karten and W. Hodos (pp. 88, 90, 92, 94, 96, 98, 100, 102, and 104), 1967, Baltimore: Johns Hopkins Press. Copyright 1967 by Johns Hopkins Press. Adapted with permission.

of the color it displayed. Finally, *correct strategy* represents the number of trials in which the subject responds to the now-correct color, alternating between pecking keys if necessary. To separate different strategic phases, the complete sequence of trials was transformed into distinct bins of 12 trials each, as the quasirandomized stimulus presentation sequence provided for equal distribution of colors to both pecking keys only within a 12-trial sequence. For each of these bins, the percentage of each strategy was calculated. This procedure enables separation of color perseveration from side perseveration and correct strategy. Finally, the percentages of the individual bins were summed up separately for each strategy, resulting in three strategy measures for each reversal

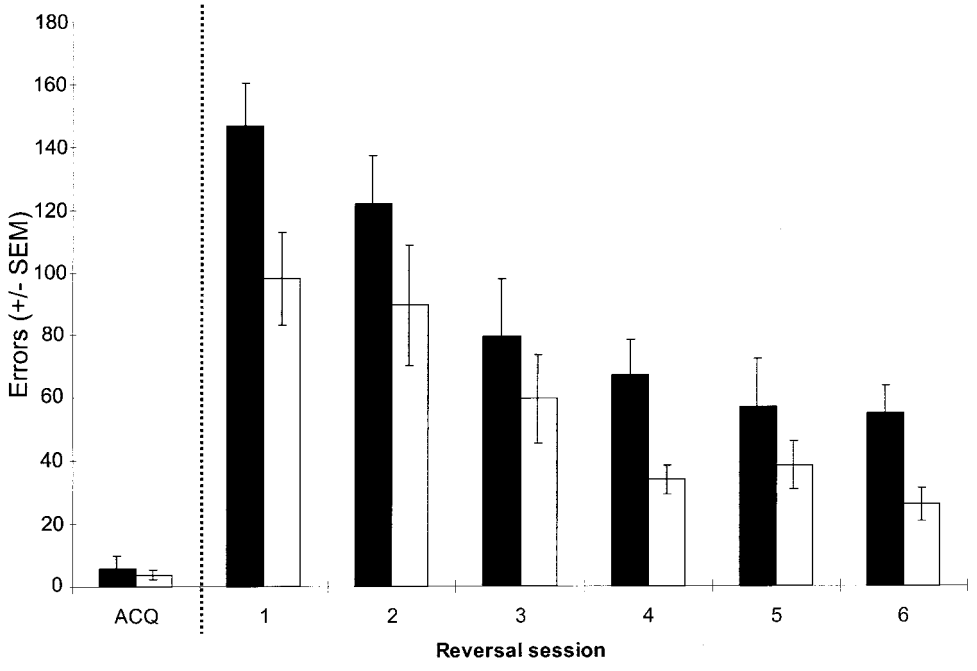

Figure 2. Mean (± *SEM*) total number of errors to criterion made by AP-5-treated (solid bars) and control (open bars) pigeons during first-time acquisition (ACQ) of the color reversal task and in the six reversal sessions.

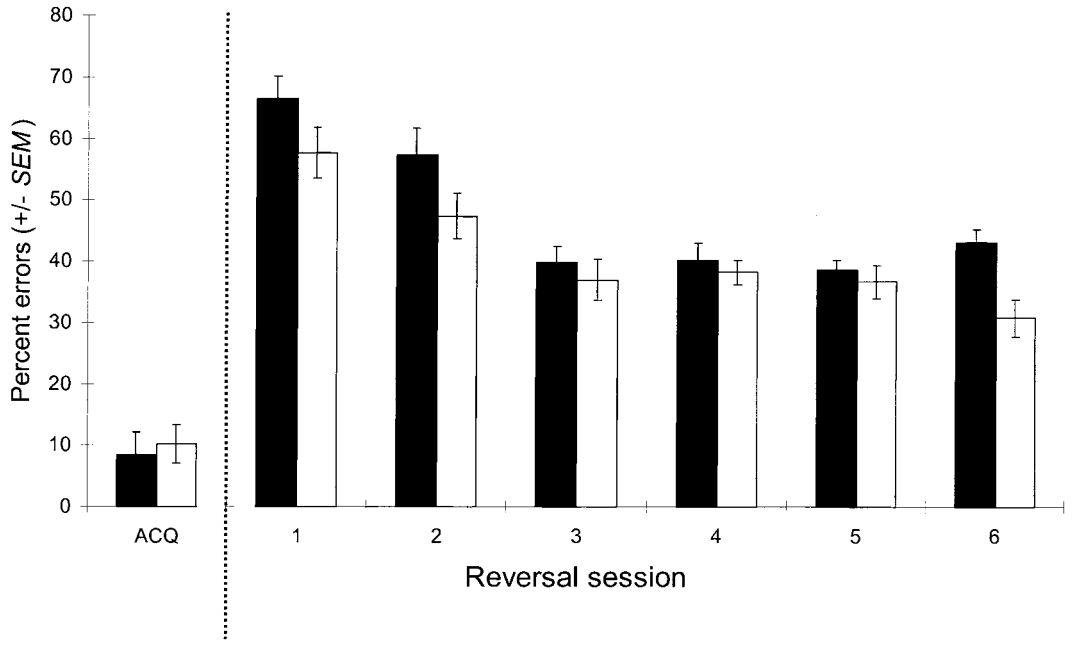

Figure 3. Mean (± *SEM*) percentage of errors relative to total number of trials made by AP-5-treated (solid bars) and control (open bars) pigeons, calculated for each session during first-time acquisition (ACQ) of the color reversal task and in six reversal sessions.

session. In the reversal sessions, all pigeons started with color perseveration. The number of trials on which this strategy was used differed significantly between groups, $F(1) = 8.09$, $p < .05$ (two-tailed), with AP-5-treated pigeons showing a considerably stronger color perseveration tendency than controls. In addition, there was a significant main effect of session, $F(5) = 31.06$, $p < .01$ (see Figure 4). Side perseveration superseded color perseveration, and for this second strategy, there was again a significant main effect of session, $F(5) = 3.30$, $p \leq .01$. Differences between groups were not significant, $F(1) = 2.04$, although the AP-5 group lingered in this phase longer than did controls (see Figure 4).

With regard to correct strategy, no significant differences between groups could be detected, nor was there a main effect of session or significant interaction (see Figure 4).

Discussion

The results of this study demonstrate similarities as well as distinct differences between the learning performance of AP-5- and vehicle-treated pigeons. First, in acquisition of the color discrimination, we observed only a slight and nonsignificant impairment of AP-5-treated pigeons compared with controls. Second, although both groups were capable of learning the color discrimination as well as the color reversal task, pigeons with temporary blockade of NMDA receptors in the NCL were significantly impaired during the color reversal learning process. Third, both groups seemed to gradually acquire a higher order strategy, enabling them to speed up their learning in later reversal learning sessions.

Impaired Color Reversal Learning

In color reversal learning, the AP-5 group displayed a significantly higher error score, which was due to their significantly increased color perseveration tendency on the S−, particularly during early reversals (1 and 2). At the same time, neither side perseveration nor correct response strategy behavior differed significantly between groups. Thus it was mainly on the previously acquired behavior that AP-5-treated pigeons showed increased perseveration despite negative feedback. It is conceivable that they were unable to use the feedback as efficiently as saline-treated pigeons did and therefore needed more examples of the altered stimulus–response–consequence configuration to learn the new association. However, after finally adopting the side strategy, AP-5-treated pigeons were undistinguishable from controls with regard to their ability to give it up again for the sake of the correct strategy. In summary, the deficit of the AP-5 group in strategy usage was not in reacting to a novel S+, but in ceasing to react to the previously learned S+. Once they "unlearned" the obsolete S+, they were as quick as controls in acquiring the novel S+.

On the other hand, NMDA receptor blockade in the NCL obviously did not influence the pigeons' performance in the first-time acquisition of a color discrimination. This dissociation in the performance of the AP-5-treated pigeons might be due to an important difference between acquisition of a color discrimination and color reversal learning: During acquisition, a completely new stimulus–response association is being formed. In color reversal, however, the new, reversed stimulus–response association has to compete with the stimulus–response association established previously. In parallel to learning something new, something previously learned must be unlearned to allow the new stimulus–response association to guide behavior. This might not merely constitute an additional learning load but might involve another type of process: extinction of a previously acquired association. Learning and unlearning, or extinction, are probably related to the neuronal mechanisms of LTP and LTD, respectively. Induction of LTP and LTD can be blocked by AP-5 in vitro (Castro-Alamancos

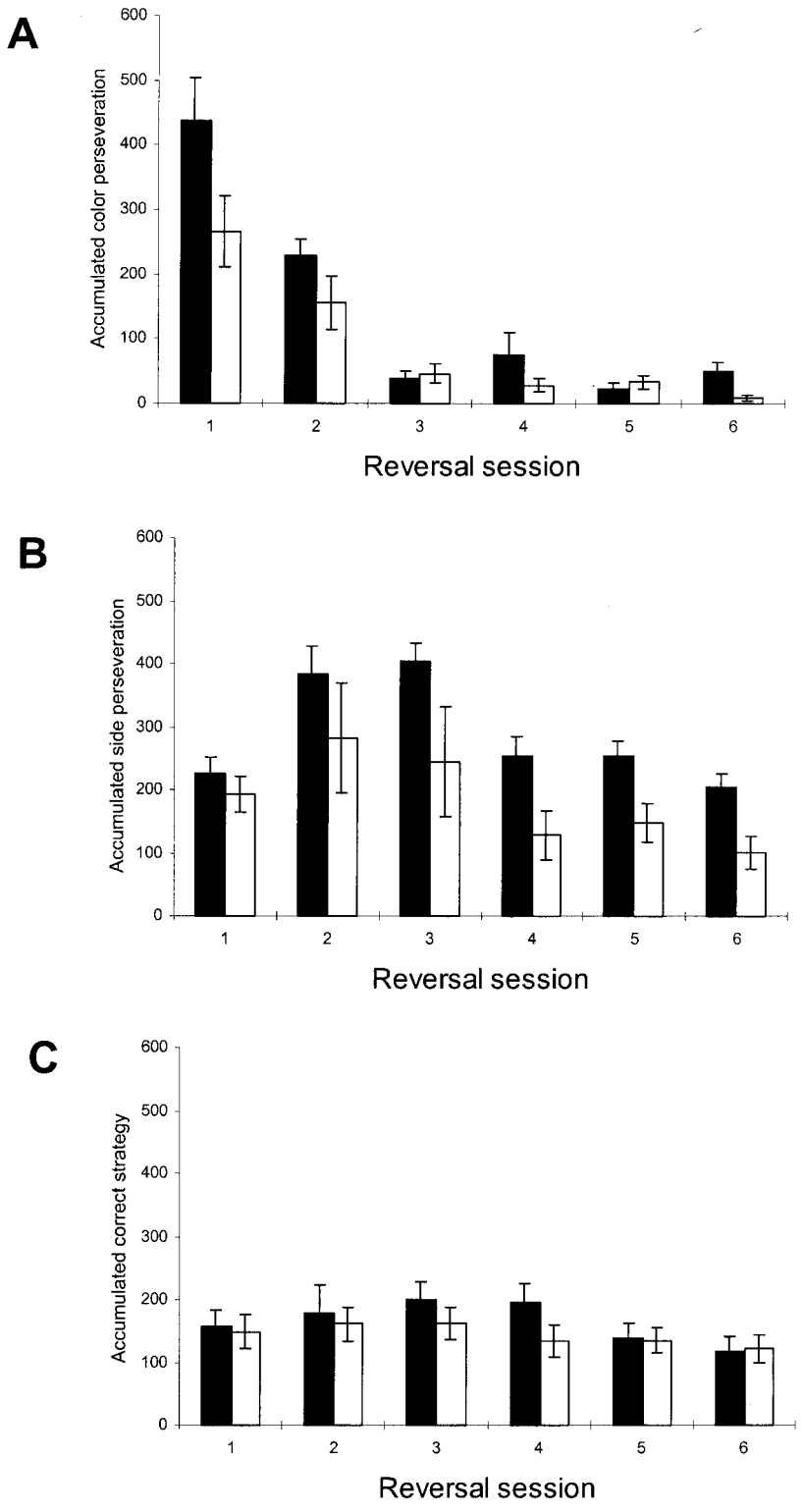

Figure 4. Mean (± *SEM*) performance in color reversal tasks by AP-5-treated (solid bars) and control (open bars) pigeons using different learning strategies. The first strategy, color perseveration (A), shows significant differences between groups, whereas side perseveration (B) and correct strategy (C) do not.

et al., 1995; Gean & Lin, 1993; Hrabetova & Sacktor, 1997), and LTP alone was shown to be blocked by AP-5 in vivo (Morris, 1989). Because there is evidence of LTP and LTD being induced by activation of distinct subpopulations of NMDA receptors (Hrabetova & Sacktor, 1997), it is conceivable that NMDA receptors take part in learning as well as in unlearning. An involvement of NMDA receptors in extinction procedures has already been demonstrated in extinction of conditioned fear, which could be blocked by local AP-5 infusions into the amygdala (Falls, Miserendino, & Davis, 1992).

The results of the present study suggest that extinction of an established response to the S− (previously S+), rather than acquisition of a response to the new S+, might be mediated by NMDA receptors in the NCL. Impaired extinction caused by NMDA receptor blockade might lead to the observed increase in perseverative behavior during reversals, but not during acquisition, in which no extinction is required. In principle, however, it is possible that initial acquisition was not affected because the synaptic rearrangements necessary took place outside the NCL, or independently of NMDA receptor functions in the NCL. Our results do not permit us to rule out this possibility. Another possibility is that the acquisition of a color discrimination is too easy to be impaired by the treatment. However, results from other studies show the NCL to also be involved in acquisition, as lesions of the NCL cause impairments in the reacquisition of a visual discrimination (Aldavert-Vera et al., 1999). In our study, AP-5-treated pigeons showed a small, nonsignificant acquisition deficit of the color discrimination task. Therefore, it is conceivable that NMDA receptors might also participate in acquisition and require LTP, although to a lesser extent than in reversal learning.

Unimpaired Learning of a Higher Order Strategy

In our study, AP-5-treated pigeons were especially impaired during the first reversal sessions, although the effect leveled out in later reversals. In an identical task, under blockade of D_1 receptors, no deficits were found during the first 25 reversal sessions; however, impairments appeared in later reversals. Thus, blockade of NMDA receptors impaired the onset of learning, whereas blockade of D_1 receptors caused deficits in later learning phases. These differential effects might reflect two different cognitive strategies (Diekamp, Prior, & Güntürkün, 1999): Whereas pigeons seemed to treat the color stimuli in the first reversal sessions as prototypical S+ or S−, signaling food or no food, they later learned that a certain color was related to food only temporarily. Therefore, the first reversal sessions seem to represent true reversals, in which the new S+ is learned and stored in long-term memory, presumably by NMDA receptor-mediated synaptic rearrangements. In later reversals, however, the pigeons seemed to keep the temporary S+ in working memory for the current session, conceivably by mechanisms involving the participation of D_1 receptors. (Güntürkün & Durstewitz, 2000; Izquierdo et al., 1998; Sawaguchi & Goldman-Rakic, 1991, 1994). Not only did the AP-5 group show this performance improvement during later reversals, but the saline group did as well. Thus, this learning-to-learn effect seems to work independently of NMDA receptor participation. To determine the correct color for the current session, pigeons used a side strategy, which presumably is a means to this end (Diekamp et al., 1999). Thus a higher order strategy, namely switching between always-present alternatives, might in later reversals replace the prior strategy of erasing one stimulus–response association and establishing another. Although erasing and establishing may require activity of NMDA receptors in the NCL, switching might work without them.

Area Specificity

To evaluate the spread of AP-5 during a pilot study, we injected 0.5 μl of the fluorescent tracer rhodamine isothiocyanate, known for its wide diffusion area, into the NCL. These cases revealed an average spread of 1 mm diameter around the tip of the cannula, ranging from 0.49 mm to 1.68 mm diameter. Therefore, injections through guide cannulas on positions L 5.00 and L 7.50 (separated by 2.50 mm) should cover the lateral–medial range of the NCL but should not extend anteriorly and posteriorly to areas outside the NCL. Similarly, diffusions into the ventricle are unlikely. Thus, the behavioral effects observed were probably not due to the spread of AP-5 to adjacent brain regions via the ventricle or the brain tissue. A study considering diffusion of AP-5 in the rat hippocampus used [3H]-AP7, which has diffusional characteristics supposedly identical to those of AP-5. It was found that with an injection volume of 1 μl (twice the volume we used per cannula), diffusion had dropped to about 50% at 1.5 mm around the actual injection site. Three millimeters around the injection site, values had dropped further, to almost 0% (Morris, Halliwell, & Bowery, 1989). These considerations are important against the background of studies showing that lesions of the Wulst result in reversal deficits (Macphail, 1971; Shimizu & Hodos, 1989). Because the posterior border of the Wulst is more than 4 mm distant from the most anteriorly situated cannulas of the present study, it is highly unlikely that AP-5 injections into the NCL affected processes within the Wulst.

For both mammals and birds, it is well known that there are various forebrain areas that, when lesioned, lead to impaired performance in reversal tasks. Thus far, our data do not imply that reversal deficits will occur only if the NCL is temporarily blocked or lesioned. They demonstrate, however, that NMDA receptors in the NCL play a key role in mediating reversal learning processes.

Summary

Taken together, the results of the present study demonstrate for the first time that NMDA receptors in the avian NCL are necessary for learning processes. It is conceivable that their effect on reversal learning involves participating in extinction of previously learned associations. In this task, impairment of their functioning is visible as perseveration on a suboptimal strategy. In a broader context, their normal functioning might be comparable to the PFC-related ability to adjust behavior to changing environmental conditions.

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