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Research report

Stimulation of dopamine D1 receptors in the avian fronto-striatal system adjusts daily cognitive fluctuations

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ABSTRACT

Several studies have shown that the level of dopaminergic transmission and D1 receptor signaling is crucial for working memory (WM) in the prefrontal cortex (PFC) of mammals. Thus, hyper- or hypostimulation of prefrontal D1 receptors are pathophysiological findings often involved in cognitive and WM impairments. These observations can be mimicked by supranormal stimulation or inhibition with D1 receptor agonists or D1 antagonists, respectively. As a consequence, it is assumed that there is a normal range of dopamine function in prefrontal cortex that can be described as an inverted U-shaped relationship between dopamine transmission, i.e. D1 receptor stimulation, and intact WM. If this is true, short-term fluctuations of cognitive performance might be described as small-scale adjustments along the tip of the inverted U-curve and should depend on D1 receptor stimulation. We tested this hypothesis in pigeons performing a delayed-matching-to-sample task (DMTS), a classic paradigm to test WM. We applied the D1 agonist SKF81297 and the D1 antagonist SCH23390 into the nidopallium caudolaterale (NCL), the avian functional analogue of the PFC, and simultaneously in the medial striatum (MSt), by in vivo microdialysis while the animals performed the task. Animals showed daily fluctuations in WM performance. While the D1 agonist was able to improve or to decrease performance during low or strong performance periods, respectively, performance did not differ from control with the D1 antagonist. This study shows that D1 receptors seem to calibrate differentially prefronto-striatal functions based on individual low or high performance states.

1. Introduction

Working memory (WM), which is the ability to hold and manipulate information online, is related to prefrontal and dopaminergic processes. Accordingly, a strong dopaminergic innervation and a high density of dopamine (DA) D1 receptors in the prefrontal cortex (PFC) [52] are crucial. The amount of released DA is positively correlated with WM performance [64]. Prefrontal DA depletion or D1-blockade in the PFC results in severe WM deficits [8,68,71,76]. Memory cells within the PFC show elevated firing patterns during delay periods of WM tasks [25] and D1 receptor agonists increase their activity during the delay [72]. Computational models suggest that DA stabilizes neural representations during WM [21,22].

The PFC is tightly connected to striatal subfields, forming prefronto-striatal loops [2]. Consequently, the striatum participates in WM performance [33,37,77] and striatal neurons respond during delays in a delayed-matching-to-sample (DMTS) task [40]. Since the striatum is a major target of DA and striatal neurons are strongly modulated by DA [62], the connections between the striatum and the PFC give an additional route for DA to influence WM.

D1 receptor functions probably modulate WM along an inverted U-shaped curve [4,10,85,89]. An optimal DA level is necessary for proper WM performance, with either hypo- or hyperdopaminergic states leading to WM impairments. Thus, prefrontal application of a low dose of a DA agonist improves WM in monkeys [86], especially in aged animals with impaired performance [9,11], while higher doses impair spatial WM in rats [89]. Also, prefrontal D1 agonists improve WM in low performing but not high performing rats [32]. In humans, oral administration of dextroamphetamine impairs WM in high performers and improves WM of low performing individuals [55].

To further investigate the role of D1 receptor signaling on individual WM fluctuations and within the pigeons prefronto-striatal system, we applied the D1 agonist SKF81297 and the D1 antagonist SCH23390 via reverse in vivo microdialysis into the nidopallium caudolaterale (NCL) and the medial striatum (MSt) while pigeons performed a DMTS-task. The NCL is considered the avian analogue of the PFC based on structural and functional levels, while the avian and mammalian MSt are homologues structures [39,66]. According to the inverse U-shaped curve of D1 receptor functions on WM, a D1

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agonist should improve WM during states of low performance and should impair WM during states of high performance, with the D1 receptor antagonist having opposite effects. It is important to know that earlier investigations observed this pattern by different types of subjects [32] or by varying a well-trained task condition in the same individuals [23], while present findings extend this showing that the D1 agonist modulates WM in opposite directions depending on different performance levels within the same individual and within the same task.

2. Material and methods

2.1. Subjects

Ten experimentally naive, adult, unsexed pigeons (*Columba livia*) of local stock were used in the experiments. They were housed in individual cages in a temperature-controlled room on a 12-h light–dark cycle. One week before training, they were food-deprived to 80% of their normal free feeding weights. They always had *ad libitum* access to water and grit. All pigeons were trained and tested 4 or 5 days a week in an operant chamber. The animal procedures were conducted in accordance with the NIH *Guide for the Care and Use of Laboratory Animals* and under adherence of the German laws to protect animals.

2.2. Apparatus and stimuli

Two identical operant chambers (34 cm × 33 cm × 36 cm) were used in the pretraining and DMTS-task. Each chamber was controlled via a digital input–output-board (CIO-PDISO8; Computer Boards, Inc.) and illuminated by a 24 W, centrally fixed light bulb. Three opaque operant keys (2 cm in diameter) with a distance of 10 cm between them were located at the back panel of each box, 22 cm above the floor. The pecking keys were homogeneously transilluminated either by white, red or green light, without matching the brightness of the colors. White lights were used in the operant conditioning and pretraining sessions, while red and green lights were used during the training and the DMTS-task. The feeder, combined with a light emitting diode, was fixed in the center of the back panel, 5 cm above the floor.

2.3. Behavioral procedures

2.3.1. Pretraining

During the first sessions, pigeons were trained to peck reliably on the center key, whenever it was illuminated with white light. After a single peck, the light was turned off, and the pigeons were reinforced with 3 s access to food, followed by an inter-trial interval for 5 s. In the next steps, each trial began with the illumination of the center key. One peck on the lateral keys during this phase terminated the trial which was then followed by an inter-trial interval of 15 s and a retry of the trial. Pecking on the central key led to the extinction of the central light and, immediately thereafter, to the illumination of one of the lateral choice keys. After pecking the illuminated lateral key, pigeons were reinforced, whereas pecking the dark choice key caused punishment by a 10 s time-out period during which all lights were turned off. One session included 80 trials with a 15 s inter-trial interval between each trial. Throughout the next training sessions, the number of pecks required on the center key to extinguish the center light and to turn on the lateral lights was constantly increased from 1, 3, 6 to 15 pecks. The criterion for the pretraining was 100% correct responses in one session.

2.3.2. Training with colored operant keys

In this phase, the operant keys were illuminated either by red or green light instead of white light. The illumination of the central stimulus with either red or green light started the trial. The center light stayed on until the pigeon had pecked the key 15 times before it was turned off. Immediately thereafter, one of the lateral keys, randomly the right or left one, was illuminated in the same color as the central key. Pigeons were reinforced after pecking the illuminated key with 3 s access to food and punished after pecking the dark key by a 10 s time-out. Training went on until the pigeons reached a performance level of 100% correct responses and were able to finish 80 trials within 20 min on three subsequent days.

2.3.3. DMTS-task

To introduce WM with a short-term memory component, we used a DMTS-task as described in earlier investigations [17]. Each trial began with the illumination of the central key, the sample stimulus, either in red or green. During this time, pecking on the lateral unlighted keys terminated the trial and an inter-trial interval was initiated followed by a repetition of the trial. Otherwise the sample stimulus remained active until the pigeon had pecked the sample stimulus 15 times. After that the delay period started during which the sample stimulus was no longer visible. At the end of the delay, the two lateral choice keys were illuminated simultaneously, one in red and the other in green light. Matching the sample stimulus by choosing the choice key lightened in the same color as the sample stimulus before with one peck (correct response) was rewarded immediately with free access to food for 3 s. Choosing the complementary color which was not shown at the previous sample stimulus (incorrect answer), was punished with a 10 s time-out period in darkness. The next trial started after a 15 s inter-trial interval. Each session consisted of 80 trials. The order in which colors were presented was randomized, so that pigeons could not learn a fixed sequence of presentation of the stimuli (Fig. 1).

Pigeons were first trained on a 0 s delay task until they reached a performance level of 80% correct matches in at least three subsequent sessions. Afterwards the delay level was augmented from 0 to 1 s delay until they reached criterion after which the delay was increased again to 2 s and later up to a maximum of a 4 s delay.

During the last eight sessions before surgery, all pigeons had to reach an overall criterion of 80% correct responses on the maximum 4 s delay. After surgery, animals were given a recovery period with no testing sessions and free access to food and water for 1 week. Then deprivation and testing started again until the birds reached the same criterion as before surgery. Upon reaching this criterion, all behavioral experiments were combined with reverse microdialysis.

2.4. Surgery

Pigeons were anaesthetized with ketavet (40 mg/kg i.m.; Upjohn) and xylazin (8 mg/kg i.m.; Rompun, Bayer). Stainless steel guide cannulae with a screw cap (NCL: 0.75 mm o.d., 14 mm in length; MSt: 0.75 mm o.d., 16 mm in length) were implanted stereotaxically, using the pigeons brain atlas from Karten and Hodos [45]. The coordinates for left NCL, as defined by Waldmann and Güntürkün [78] were A: 5.0; L: 7.5; V: 1.0 and for left MSt A: 11.0; L: 2.5; V: 5.7. Guide cannulae were fixed with dental acrylic and temporarily closed with a wire to prevent infections. For reversed in vivo microdialysis implants were made unilateral because our established system did not enable us to implant cannulae in the MSt of both hemispheres. Hence, implants were made unilateral in the left hemisphere, as memory traces are mostly left hemisphere-based [35]. After surgery, the animals were moved back into their cages and allowed to recover for 5 days with free access to food and water.

2.5. In vivo microdialysis and drugs

Self-made concentric microdialysis probes had a dialysis membrane of regenerated cellulose (i.d. 215 μm, o.d. 251 μm, membrane thickness 18 μm, cut-off 6 kDa; Akzo, Wuppertal, Germany) glued to a stainless steel cannula (19 mm in length, 26 G, i.d. 305 μm, o.d. 508 μm; Small Parts, Miami, USA). The total length of the membrane was 3.3 mm, with an effective length of the active membrane of 2.5 mm (0.4 mm at the beginning and at the end were glue sealed). A polyethylene tube (i.d. 510 μm, o.d. 1500 μm; Kleinfeld Labortechnik GmbH, Gehrden, Germany) was fixed to the end of the stainless steel cannula and served as inlet. A fused silica capillary inside the probe (i.d. 75 μm, o.d. 150 μm; Cil Cluzeau, Sainte Foy la Grande, France) covered with a polyethylene tube (i.d. 280 μm, o.d. 600 μm; Kleinfeld Labortechnik GmbH, Gehrden, Germany) served as outlet.

The selective D1-like agonist SKF81297 hydrobromide (RBI Natick, MD, USA) and the selective D1-like antagonist SCH23390 hydrochloride (RBI Natick) were dissolved in Ringer solution at a concentration of 10 μM [75]. Both drugs have an activity comparable with DA itself [73] and higher doses up to 1 mM of SCH23390 lead to sedation and motor impairments [1], while excessive stimulation via D1 receptors agents leads to higher locomotor activity [6]. As reviewed by Castner and Williams stimulation or blockade of D1 receptors produces an inverted U-shaped function of working memory in a dose-dependent manner. Because drugs were constantly infused into the fronto-striatal system during the task, we decided to choose the concentration of 10 μM for both drugs which had proved effective at the electrophysiological level [75,30] and previously successfully altered behavior at a lower concentration after injecting into the NCL, but did not produce motor or motivational deficits after intraPFC/NCL infusions [16,89,32]. Pharmacological migration of the infused compounds was not detected, and concentrations of dopaminergic drugs needed to be relatively high (up to 10 mM) to reach substantial brain concentration at a distance of 1 mm from the microdiaylsis probe [84]. Conclusively, it is unlikely that the D1 agonist or the D1 antagonist spread far into surrounding structures like from the NCL into the overlaying lateroventral hippocampus complex (CDL, area corticoidea dorsolateralis), or into the medial nidopallium caudale and from the MSt into the nucleus accumbens and the Nidopallium. The stock solution of SCH23390 and SKF81297 was aliquoted in Eppendorf tubes and frozen at −80 °C for later use. Ringer solution (Fresenius GmbH, Bad Homburg, Germany) was used in control sessions.

For reversed in vivo microdialysis pigeons were transferred into the operant chamber. The microdialysis probes were inserted into the guide cannulae of the NCL and MSt and connected via a dual-channel-Swivel (Axel Semrau GmbH & Co, Germany) with a microinfusion pump (PHD 2000 Infusion, Harvard Apparatus). The swivel was fixed on a freely moving arm on the top of the chamber to allow the pigeons for moving. Microsyringes (1 ml, CMA, Wuppertal, Germany) were used to perfuse the drugs or Ringer solution constantly at a flow rate of 1 μl/min. No dialysates were collected in our experiments. After inserting the probes, perfusion started immediately and pigeons were given a 15 min habituation period before testing sessions started. On day one and three of each week only Ringer solution was infused through reverse microdialysis while pigeons performed the DMTS-task. On

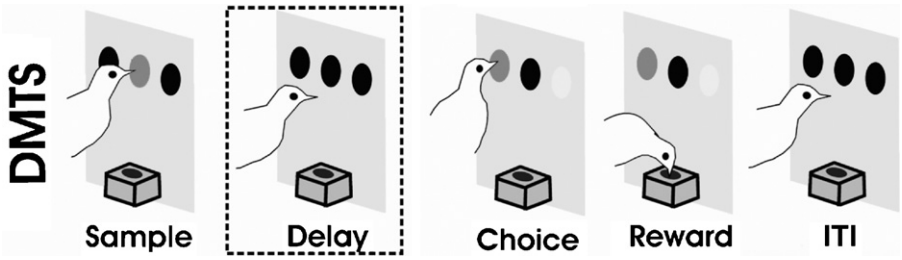

Fig. 1. Schematic illustration of the delayed-matching-to-sample task. Each trial started with the presentation of either a green (light grey) or red (dark grey) stimulus as SAMPLE on the central key. After 15 pecks a 4-s DELAY period started in which the animals had to hold information about the stimulus online. Then the side keys lit, starting the CHOICE period. After a correct choice a 3-s REWARD phase began, followed by a 15-s inter-trial interval (ITI).

day two and four either SKF81297 or SCH23390 were infused in a balanced design and in randomized order among the pigeons. On each experimental day animals had to perform two DMTS sessions consisting of 80 trials each. Animals were tested on four consecutive days per week over a period of 4 weeks, except for two animals who were tested for 2 and 3 weeks only. At the end of each experimental day, the microdialysis probes were removed and the guide cannulae were resealed with a wire. Pigeons were then transferred back into their cages.

2.6. Histology and reconstruction of the cannula positions

After the experiments, pigeons were injected with heparin (1.000 IU, i.m.) 15 min before they were deeply anaesthetized with Equithesin (0.5 ml/100 g body weight, i.m.) and perfused intracardially with 0.9% saline followed by a 4% phosphate-buffered paraformaldehyde solution. Brains were removed, sectioned into 40 μm frontal slices and stained with cresyl violet following standard histological procedures. Positions of the guide cannulae in the left NCL and left MSt were histological verified and determined according to the atlas of Karten and Hodos and the anatomic division of the NCL as defined by Waldmann and Güntürkün. Photographs were taken with an AxioCam color camera attached to an Olympus BH2 microscope. Digital images were edited with Adobe® Photoshop 5.5.

Histological analysis confirmed the correct positioning of all cannulae in NCL and MSt (Fig. 2).

2.7. Data analysis

2.7.1. Behavior

The behavior during each DMTS session was analyzed in terms of overall performance, i.e. percent correct responses, reaction time, i.e. the time between onset

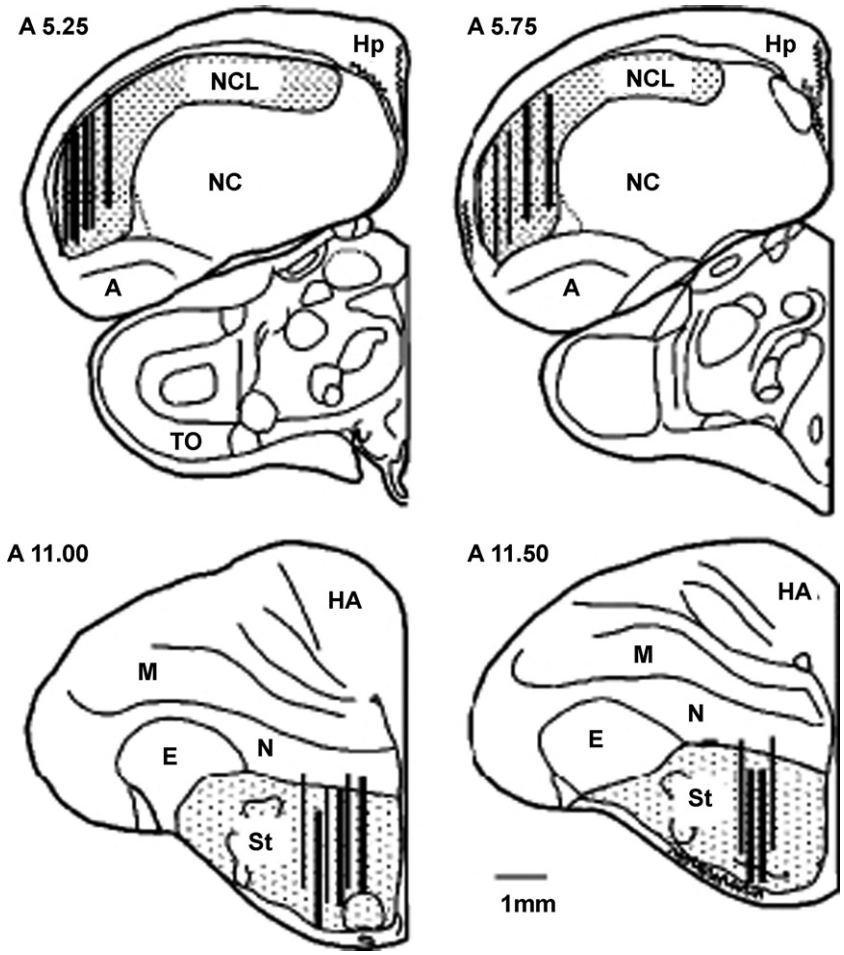

Fig. 2. Location of microdialysis probes in the left nidopallium caudolaterale (NCL) and left medial striatum (MSt) in schematic coronal sections of the pigeon brain (Karten and Hodos [45]). The anterior distance from the zero point is labeled in each of the four sections. The areas of the active membranes of the dialysis probes are indicated by black lines in NCL and MSt. *Abbreviations*: A, Arcopallium, E, ectopallium; HA, hyperpallium accessorium; Hp, hippocampus; M, mesopallium; N, nidopallium; Nc, nidopallium caudale; TO, tectum opticum.

of the two lateral choice keys and the time of the first peck to either the matching or non-matching choice key, and overall session time, i.e. time between the onset of the first trial and end of the trial 80. These measures were calculated for each session.

For each animal, the median performance was calculated over all control sessions which were conducted during infusion with Ringer solution. This median characterizes the performance of each individual over several sessions and weeks. But performance of the animals varied from week to week. Thus, for each individual the median performance during control sessions in 1 week was compared with the median derived from all control sessions. If the weekly median performance was above the overall median performance, all data collected during that week were considered to be collected while the animal was in a high performance state. When the weekly median performance was below the overall median performance, then data were taken during the animal's low performance state.

For further analysis, all behavioral data (performance, reaction time, overall time) from each individual were averaged over low performance states and high performance states. Effects of the infusion of Ringer, SKF81297 or SCH23390 on the behavioral measures were analyzed by parametric ANOVAs, followed by Fisher LSD tests for post hoc analysis. To be able to directly compare the effects of SKF81297 or SCH23390 infusions during low and high states of performance, performance levels were normalized to the weekly performance, which was set to 100%. The relative percent differences between the performances under control conditions (100%) versus treatment conditions under low and high states of performance were then analyzed by parametric ANOVAs. Fisher LSD tests were used for post hoc analysis. The level of significance was set at $p < 0.05$.

3. Results

In control sessions, under infusion of Ringer solution, all 10 pigeons performed the DMTS-task on average at a performance level of $84.86 \pm 11.40\%$ (mean ± S.D.) (Fig. 3). Reaction times in seconds were 1.22 ± 0.36 s and control sessions lasted on average 4621.93 ± 4856.72 s.

All behavioral data were analyzed based on the distinction between low and high states of performance. For the performance levels, the ANOVA revealed significant differences between treatment and states ($F_{(2,36)} = 19.712$, $p < 0.001$).

Performance levels in control sessions during low periods were $82.56 \pm 9.14\%$ correct responses and during the strong periods $91.56 \pm 7.19\%$ correct responses. As expected these performance levels differed significantly ($p < 0.024$, Fisher LSD).

Performance levels in the low state under infusion of the D1 agonist SKF81297 were $86.88 \pm 9.43\%$ correct responses and in the high state $89.25 \pm 6.75\%$ correct responses. Post hoc analysis with Fisher LSD tests showed significant differences between these levels to those in the control condition (low: $p < 0.001$; high: $p < 0.02$).

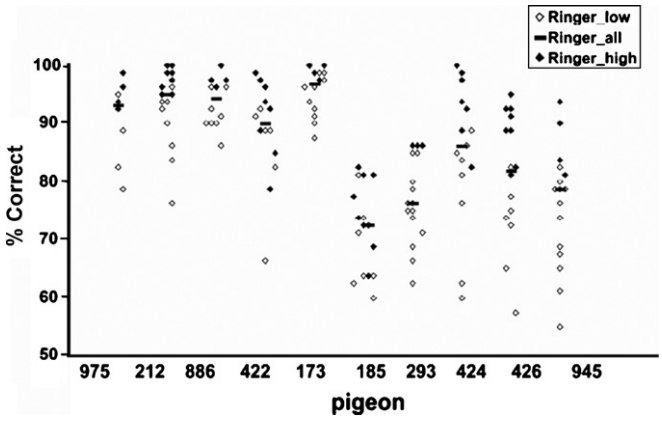

Fig. 3. Median percent correct answers in the DMTS-task for each pigeon during infusion of vehicle (Ringer solution) into the NCL and the MSt. The black bar represent the median of all control sessions (Ringer_all), black squares represent the percentage correct in control sessions in high (Ringer_high) and white squares represent the percentage correct during low (Ringer_low) performing periods. Numbers represent animals. As depicted, performances of animals varied widely in each and between animals.

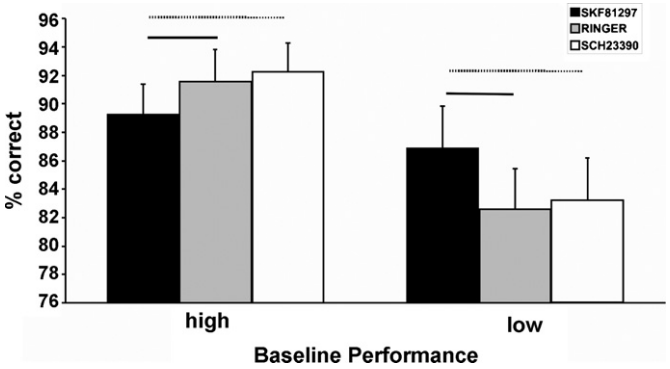

Fig. 4. Percent correct answers in the DMTS-task in high (left) and low (right) performing periods under administration of the D1 agonist SKF81297 and the D1 antagonist SCH23390 in comparison to vehicle (Ringer). Error bars represent standard error means ($n = 10$ pigeons). Lines or dotted lines represent significant differences.

Performance levels in the low state under infusion of the D1 antagonist SCH23390 were $83.19 \pm 9.38\%$ correct responses and in the high state $92.18 \pm 6.43\%$ correct responses. Post hoc analysis with Fisher LSD tests showed no differences between these levels to those in the control condition (low: $p = 0.48$; high: $p = 0.48$) (Fig. 4).

To analyze directly the effects of SCH23390 and SKF81297 between low and high states of performance, performance levels were normalized to the baseline condition. The relative differences of the percent correct responses under infusion of either SKF 81297 or SCH23390 to baseline (Ringer infusion) were calculated. The ANOVA revealed significant differences between states ($F_{(1,18)} = 6.389$, $p = 0.021$) and treatment and states on the relative differences in % correct responses ($F_{(1,18)} = 32.893$, $p < 0.001$). In the low period, the relative differences in % correct performance under infusion of SCH23390 were $0.79 \pm 3.54\%$ and under infusion of SKF81297 $5.32 \pm 4.51\%$. So performance levels in the DMTS-task were enhanced under infusion of SKF81297 ($p = 0.002$, Fisher LSD). In the high state, the relative differences in % correct responses under infusion of SCH23390 were $0.80 \pm 3.16\%$ and under infusion of SKF81297 $-2.01 \pm 2.71\%$. Under this state SKF 81297 impaired the performance in the DMTS-task ($p = 0.006$, Fisher LSD). The post hoc analyses showed also a significant difference between changes by SKF81297 in high and low states ($p < 0.001$), while these effect could be not observed for SCH23390 ($p = 0.998$) (Fig. 5).

The ANOVA revealed no differences between low and high performance states in terms of reaction times between treatment and state ($F_{(2,28)} = 1.569$, $p = 0.226$). The reaction times under infu-

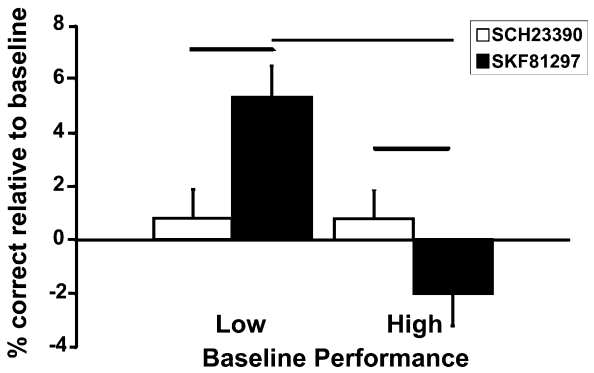

Fig. 5. Differences in correct responses relative to baseline (set to 100%) in the DMTS-task under prefronto-striatal infusions of SCH23390 and SKF81297. Error bars represent standard error means ($n = 10$ pigeons). Lines or dotted lines represent significant differences.

sion of Ringer were 1.15 ± 0.28 s in the low and 1.34 ± 0.36 s in the high state. The reaction times under infusion of SCH23390 were 1.16 ± 0.31 s in the low and 1.24 ± 0.35 s in the high state or SKF81297 were 1.17 ± 0.26 s in the low and 1.24 ± 0.41 s in the high state. Due to technical reasons, reaction times of only EIGHT pigeons could be included in the analyses.

No differences in the overall session times under infusion of Ringer (low: 3805.04 ± 2166.00 s, high: 3124.85 ± 803.94 s) or SCH23390 (low: 3606.80 ± 2205.15 s, high: 3033.65 ± 1073.14 s) or SKF81297 (low: 3777.61 ± 1780.89 s, high: 2902.18 ± 807.34 s) could be detected with the ANOVA ($F_{(2,36)} = 0.182$, $p = 0.834$).

4. Discussion

The present study reveals that the D1 agonist SKF81297 increased WM performance in a delay-matching-to-sample task during low cognitive performance states when administrated into the prefronto-striatal system of the pigeon. This effect was reversed when infusions were administered during high cognitive performance states. Thus, the effect of the D1 agonist was dependent on the cognitive state of the animals. Infusions of the D1 antagonist SCH23390 had no effect. Overall, agonistic D1 receptor stimulation can decrease or enhance cognitive performance, dependent on the cognitive baseline performance state of the individual. These data support the assumption that the effect of D1 receptor stimulation on WM follows an inverted U-curve [89].

Numerous studies in pigeons [17,42,44,69,83,87] and other animals, including humans [12–14,19,26,51,57,81,86] have shown that WM as tested with delay tasks depend on DA transmission within the prefronto-striatal system. Earlier investigations reported that blockade of D1 receptors in the mPFC of rats only impaired attentional accuracy in rats that displayed high levels of baseline performance. Moreover, infusion of the D1 receptor agonist SKF 38393 caused the opposite effect, improving performance in subjects whose baseline levels of attentional accuracy were low [32]. In addition, performance in trials with longer delays was improved by SKF81297 in subjects with low baseline performance, while it was deteriorated in trials with shorter delays in high performing rats [23]. Those differences in baseline performance were explained by the finding of Phillips et al. [64] that the magnitude of DA-efflux in the PFC in a delayed-response task is predictive for the accuracy of recall after different delay-periods, with lower levels of DA-efflux associated with poorer performance. The present findings extend these results by using the within-subject variability of well-trained pigeons. We show that infusion of the D1 receptor agonist SKF81297 within the prefronto-striatal system produce contrasting results in WM performance that are opposite to the current cognitive performance state of the individual. As mentioned above, fluctuations in baseline performance possibly reflect different dopamine levels in the NCL and the MSt at different time courses, leading to suboptimal levels of D1 stimulation in the low state and exerting improvements in performance after exogenous infusion of a D1 agonist. At a high state, i.e. DA transmission is optimal, additional stimulation of D1 receptors can exert a number of actions on pre- and postsynaptic neurons that lead to a reduction of neural excitability in the PFC and WM deficits [85,88]. This in turn leads to the inverted U-shaped function of D1 stimulation and WM performance [89].

In contrast to the effects of the D1 agonist SKF81297 (10 μM), prefronto-striatal infusions of the D1 antagonist SCH23390 at the same dose produced no performance alterations. One reason for the lack of direct influence on performance could be the low dose of SCH23390. However, earlier investigations applying the D1 antagonist in a 10-fold lower concentration in the NCL during a reversal task, which also recruits prefronto-striatal circuitry, resulted in impairments in the task [16]. Additionally, studies with reverse microdialysis reported effects of SCH23390 with concentrations varying from 10 nM [63] up to 100 μM [70]. But depending on the recovery of the microdialysis probes [7] drug concentrations could vary. In contrast to the D1 blocking effects of SCH23390, DA release is increased in the fronto-striatal system during the DMTS-task [44] and SCH23390 can act as an antagonist at 5-HT2 receptors, which also increases cortical DA release [59]. Therefore, it is conceivable that the low dose of the D1 antagonist used in our study was not sufficient to induce cognitive decline in the DMTS-task.

Lesions of the striatum and the PFC led to deficits in WM [18,28,38] or changed neuronal activity in these regions during delayed response tasks [24]. The loss of brain DA like in Parkinson's disease led to impairments in fronto-striatal cognitive function, resulting in WM deficits [50]. As D1 receptor signaling in the PFC and the striatum is central to working memory [29], it is likely that functional connectivity between these areas can be influenced by D1 receptor manipulation. Both areas are highly connected via the prefronto-striatal loop [2,15,58]. Similar to mammals, lesions of the NCL in pigeons resulted in delay specific deficits [17], whereas lesions in the MSt produced deficits in cognitive flexibility [83]. Both areas have a high density of D1 receptors [20] and the connectivity between the NCL and the MSt resembles those in mammals [48,65]. One possible route to influence the inputs to the frontal cortex via the striatum is the dopaminergic signaling. Manipulations of the dopaminergic system in the PFC by 6-OHDA lesions influenced the DA level in the striatum [68]. Furthermore, DA is increased in both, PFC/NCL and striatum during WM experiments [44,51,57,64,81]. Computational studies suggest that DA controls a bistable up or down state in striatal activity, which possibly prevents alterations of prefrontal activity due to internal noise [33,37]. Hence, we assume that the interplay of the dopaminergic systems between the PFC/NCL and the striatum in the prefronto-striatal loop is critical for cognitive performance during WM. Therefore in this study, we decided to manipulate the whole system and investigate the effects of D1 stimulation or antagonism during WM in the prefronto-striatal network. This approach is supported by a recent finding from Cools et al. [14], showing that the WM performance is predictable by the DA level in the striatum like in the PFC, with good performance at high DA levels and poor performance at low DA levels. Furthermore, Nagano-Saito et al. [61] demonstrated that DA depletion impairs the prefronto-striatal network during WM by eliminating functional connectivity between these regions.

The individual WM performances of our pigeons were not constant over time. Although all animals performed the DMTS-task on a reasonably high level, they nevertheless showed daily/weekly cognitive fluctuations. Depending on their current state, stimulation of the prefronto-striatal system with the D1 agonist SKF81297 shifted their performance level up or down. Presently, we can only speculate about the causes of the daily/weekly fluctuations. For example, glucocorticoid levels could differ between treatments. It is known that their suppression impairs WM through a D1 receptor mediated hypodopaminergic mechanism in the PFC [60]. Similarly, according to circadian rhythm or genetic background of the individual DA transmission fluctuates over days or weeks [26,27,55,56].

Alterations of motivation are a possible further cause for cognitive fluctuations. We always took care to keep food deprivation levels constant, but motivation can still vary over time. In the dorsolateral PFC, neuronal activity reflects both WM and reward expectancy [79,80]. Delay-related activity is modulated in a quantitative fashion, such that a larger reward leads to increased delay-related activity relative to a smaller reward [49]. Additional studies suggest that motivational information not only modulates PFC cellular activity, but both cognition and motivation are integrated at single-cell level in the lateral PFC [47,46]. Thus, the activity

of prefrontal neurons does not only code motivational aspects, but rather codes the reward within the context of rewarding [82]. As DA release in the PFC is increased during both reward and retrieval of trial specific information [64,67,74] fluctuations in DA concentrations can also influence motivational aspects and, thus, affect performance. However, Goto and Grace [31] showed that alternations of DA release in the nucleus accumbens influence hippocampal or PFC evoked responses in the accumbens interacting with goal-directed behavior. Since these fluctuations are mainly controlled by the midbrain-accumbens projections, they are outside of the influence area of our dialysis probes [3]. Thus, it is likely that our manipulations primarily affected the cognitive aspect of the task, while motivational fluctuations influences were modulated via limbic projections.

Like the PFC, the NCL is a higher order association area and is closely tied to all secondary sensory and motor structures [48]. The NCL receives a rich dopaminergic innervation [20] and resembles the PFC with respect to its connections with the amygdala, the nucleus accumbens, and visceral structures [3,48]. The PFC is known to serve complex functions that are usually subsumed under the term 'executive control'. Similarly, the NCL was also shown to mediate various aspects of executive functions like working memory [17], reversal learning [36], delayed alternation [34], extinction learning [53], timing [41], and response selection [54]. Single unit recordings in NCL reveal cells that code for active working memory [69], reward amount [43], and subjective reward value [42]. Similarly, neurochemical experiments reveal that dopamine within NCL is released during short-term memory [44] in a volume transmission mode, that means DA diffuses from the point of release through the extracellular space to distant non-synaptic receptor sites [5]. Taken together, the mammalian PFC and the avian NCL show an astonishing degree of resemblance in terms of anatomical, cognitive, electrophysiological, and neurochemical characteristics. Based on topographical and genetic arguments [35], however, they do not seem to be homologous as a telencephalic entity within the pallium but probably represent a case of evolutionary convergence. Thus, the PFC and the NCL are functional analogues. Due to these functional equivalences, we assume that our data from pigeons also to apply to dopaminergic mechanisms in mammals.

The present results show that fluctuations in cognitive performance are adjustable via D1 receptor stimulation. The effect of D1 receptor manipulation depends on the different baseline performance level of the individual. Here, it is shown that factors determining these baseline differences in performance need not to be necessarily age [11] or general learning performance [32]. In fact, it seems to be that cognitive skills underlie dynamical processes, which are possibly controlled by DA in the prefrontostriatal connectivity. This implicates that to increase or manipulate these skills further tests to determine the baseline level are required.

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