

THE ROLE OF DOPAMINE IN MAINTENANCE AND DISTRACTABILITY OF ATTENTION IN THE “PREFRONTAL CORTEX” OF PIGEONS

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Abstract—Selective attention is a crucial component of all sensory processing. Here we test the role of dopamine in attentional selection and in the maintenance of attention. Pigeons were trained on a moving-dot paradigm comparable to the shell game. In this paradigm, pigeons had to select a target among distractors and maintain attention to the target. Target and distractors consisted of white dots, moving at random on a touch-screen. In this task, the demand on attention was modulated by varying the number of distractors and the duration of motion. Both manipulations affected performance equally. In the next step, we investigated the contribution of dopamine to attention. Intracranial injections of D1-antagonist (Sch23390) before testing led to decrements in performance that equally affected trials with different attentional demand. This drop in performance cannot be attributed to altered motivation or motor performance. We conclude that dopamine has a critical role in attention. It is involved in the selection of targets for attention and in the stabilization of attention against interference. This is comparable to the role dopamine plays in working memory and argues for similar mechanisms underlying selective attention and working memory. © 2010 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: working memory, avian, nidopallium caudolaterale.

We are all well aware of the limited capacity of our brains when it comes to processing the near unlimited amount of available sensory information. Clearly, our brains are constantly directing attention towards relevant stimuli while most sensory information is disregarded as irrelevant. Unsurprisingly, research on attention has a long tradition in neuroscience and its importance was already noted in the 19th century by William James (James, 1890). Several psychiatric disorders cause impairments in attention; the most prominent examples are Schizophrenia and attention-deficit hyperactivity disorder, a condition characterized by inattentiveness, increased impulsivity and hyperactivity (Nieoullon, 2002). Pharmaceutical therapy of such disor-

ders commonly targets the cerebral monoamine systems, in the case of attention-deficit hyperactivity disorder usually by inhibiting the monoamine-reuptake and thereby increasing the availability of dopamine and noradrenaline (Vaidya and Lee, 2009).

Dopamine is a key neurotransmitter in the regulation of motor and limbic functions and it is often seen in the light of reward processing, learning and working memory (Durstewitz et al., 2000; Schultz, 2007). Working memory is the neural system for active maintenance and manipulation of information over short periods of time (Nieoullon, 2002; Seamans and Yang, 2004) and several lines of evidence indicate that dopamine in the prefrontal cortex (PFC) plays a key role in working memory. Microdialysis showed that the prefrontal dopamine-level is modulated by the maintenance of information (Watanabe et al., 1997; Karakuyu et al., 2007); injections of dopamine-ligands demonstrated an inverted “U-shaped” response-curve with too little or too much dopamine being equally detrimental to performance (Zahrt et al., 1997); iontophoresis was used to show that the tuning of neurons engaging in maintenance of information is modulated by dopamine (Sawaguchi, 2001). Working memory models based on dopamine-function include a gating function (Braver and Cohen, 2000), the protection against interference (Durstewitz et al., 2000) and attentional selection (Awh and Jonides, 2001). Given this role in working memory, dopamine is a prime candidate for the modulation of attention. The constraints on attention and on working memory are largely similar. Both systems require the selection of targets from distractors and the stabilization of neural activity against sensory interference. Conversely, the functional anatomy of working memory and of attention shows considerable overlap (Postle et al., 2004) which led to the idea that working memory relies on processes also serving attention. By this account, the attention-network can engage in the rehearsal of information thereby giving rise to active working memory (for review see Awh and Jonides, 2001). This implies that working memory requires attention while attention does not necessarily require working memory. Further evidence for an involvement of dopamine in attention comes from the effectiveness of Methylphenidate, an inhibitor of the dopamine-transporter, in the treatment of attention-deficit hyperactivity disorder (Volkow et al., 2005). Furthermore, Granon et al. (2000) showed recently that attention can be benefit or be hindered by specific manipulations of dopamine function in rats.

Here we investigate the role of dopamine in the nidopallium caudolaterale (NCL) of pigeons while the animals perform in a novel attention-task. The avian NCL is con-

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Abbreviations: NCL, nidopallium caudolaterale; PFC, prefrontal cortex.

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sidered functionally equivalent to the mammalian PFC (Güntürkün, 2005a) and like the PFC, NCL is involved in working memory (Diekamp et al., 2002), executive control (Rose and Colombo, 2005), categorization (Kirsch et al., 2009) and the evaluation of rewards (Kalenscher et al., 2005). In the present study, pigeons performed in an attention paradigm comparable to the shell game. The animals selected a target from within several distractors and had to attend to the target for a few seconds while target and distractors randomly moved on a screen. We developed this task to reveal attention as a performance variable, as opposed to a learning-rate parameter. Before each test session, the animals received intracranial injections to the NCL, either of saline or of the D1-receptor antagonist Sch23390.

EXPERIMENTAL PROCEDURES

Subjects

We used eight adult homing pigeons (*Columba livia*) as subjects. Their weights ranged between 350 and 400 g. The pigeons were individually housed in wire mesh cages inside a colony-room and were maintained on a 12:12h light:dark cycle, with lights on at 8 AM. During the experiments, the subjects were fed with mixed grain; they were kept at 80–85% of their free-feeding weights and had free access to water. All experiments were in accordance with the National Institute of Health guidelines for the care and use of laboratory animals and were approved by a national committee (North Rhine-Westphalia, Germany).

Apparatus

The experiment was conducted in a custom-made operant chamber (35×35×35 cm³) with touch-screen monitor (Elo, TT-15.0ELXPAU), two houselights and a feeder. The touch-screen was mounted to one side of the chamber and an opening allowed the subjects to access the entire screen-area (15"). The feeder was situated below the touch-screen and gave access to a set quantity of millet as a reward. The entire setup was controlled in Matlab (The Mathworks inc.) using the Biopsychology Toolbox (Rose et al., 2008).

Training

The animals were trained in a moving-dot paradigm that was based on the shell-game. In an autoshaping-procedure (free reward after 2 s stimulus presentation or after the first peck to the stimulus), the animals were first trained to respond to a red square (1.5×1.5 cm²) displayed in the center of a square field on the touch-screen (15×15 cm², blue frame filled in black). As soon as the animals responded to the red square they were transferred to a fixed-ratio schedule (FR1). In the next step of training, a single response to the red square turned it white and the first peck to this new, white square was rewarded. Once this behavior was established, the animals were transferred to the moving-dot paradigm.

In the moving-dot paradigm, the subjects attended to a target over varying durations and identified it among distractors (Fig. 1). An inter-trial interval of 20 s was followed by presentation of the red square, which later served as target. Around this initial stimulus either 2, 5 or 11 white squares of equal size were scattered. These squares later served as distractors. A single peck to the red square turned it white, thereby rendering it indistinguishable from the distractors. At the same instance, all squares started to move around the field in a randomized fashion. Upon contact with each other or with the border of the field, squares bounced off. The motion-period lasted for either 2, 4 or 8 s after which the entire

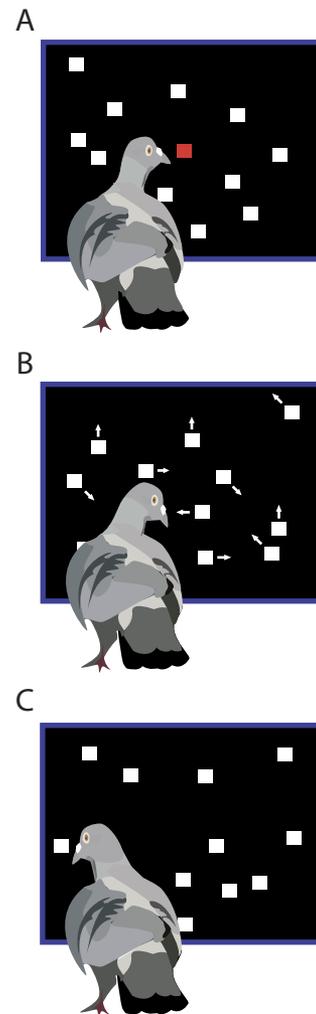


Fig. 1. The behavioral paradigm inspired by the shell game. (A) Following an inter-trial interval a red square is presented in the center of the screen; this stimulus later serves as the target. Surrounding the target, a variable number of distractors are displayed at random locations. (B) A single response to the target causes it to become white and thus optically indistinguishable from the distractors. Simultaneously, all squares start to move in randomized directions. (C) After a varying duration, the entire scene comes to a halt. A single response to the target (the square that was red before the motion-period) is rewarded with access to food. A single response to any distractor or to the background is mildly punished. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

display came to a halt. Failure to start the motion by pecking on the initial red stimulus resulted in mild punishment of 5 s lights off and terminated the trial. Responses during the motion-period did not result in reinforcement. The critical period was after movement offset, when a single peck to the target-stimulus resulted in reward-delivery while a single peck to any distractor or to the background resulted in mild punishment (5 s lights off). Placement of the distractors and the directions of motion were randomized on every trial, the order of trials was randomized for every session (72 trials).

Surgery

Prior to testing, the animals were chronically implanted with intracranial cannulas (Plastics One inc., C315G, 6 mm) plus dummy

cannulas (Plastics One inc., C315DC). Surgery was conducted under full anesthesia using 1 ml/kg (i.m.) of a 7:3 mixture of ketamine (Pfizer Pharma GmbH, Ketavet) and xylazine (Bayer GmbH, Rompun). The animals were placed in a stereotaxic frame whereupon a topical anesthetic was applied to the scalp, which was then cut and retracted to expose the skull. Small craniotomies were drilled bilaterally above the NCL at AP: 5.5, ML: ± 7.5 , DV: 3.0 (Karten and Hodos, 1967). The dura was carefully removed and the cannulas lowered into the brain. The craniotomies were then sealed using medical silicone (Dreve Otoplastic GmbH, Bipor AB) and four stainless steel screws were driven into the skull. The cannulas were attached to the screws using dental acrylic and the wound was sutured close. After surgery the pigeons were allowed to recover for at least 5 days.

Testing and injections

Once the animals reached a stable post-operative performance, testing and intracranial injections began. With respect to the behavioral protocol, test sessions were identical to training sessions. Before each test session, the dummy-cannulas were removed and injection-cannulas (Plastics One inc., C315I, 6.5 mm) were lowered into the chronically implanted guides. Attached to the injection cannulas was a tubing system (Plastics One inc., C313C) with two syringes (Hamilton, Microliter 701, 10 μ l). For injections the syringes were placed in a microinjection pump (Harvard Apparatus, PHD 2000).

Pigeons were bilaterally injected with either 1 μ l Sch23390 (3 μ g/1 μ l saline with 1% dimethyl sulfoxide for solubility) or 1 μ l vehicle (physiological saline with 1% dimethyl sulfoxide) per hemisphere. Sch23390 is a standard selective antagonist against the D1-group of dopamine receptors (K_i values for dopamine receptors are D1: ~ 0.2 , D5: ~ 0.3 , D2: ~ 1100 , D3: ~ 800 and D4: ~ 3000 nM). We used this dose/concentration since it previously proved effective for injections to the striatum of pigeons without producing any sedative effects (Acerbo and Delius, 2004). Injections were performed over 5 min at a rate of 0.2 μ l/min. The success of each injection was monitored using a minute air-bubble introduced to the system just above the injection cannula. The injection-system was removed 5 min after the injections were completed to allow full diffusion of the drugs. After injection, the pigeons were transferred to the operant chamber and set to the task as described above. Each pigeon received a total five injections of Sch23390 and five injections of vehicle. Injections of Sch23390 and of vehicle were performed alternating, interrupted by at least one day of training without any injections. After each animal had received five injections of Sch23390 and five injections of vehicle, the animals were decapitated. Brains were fixated in paraformaldehyde (4% paraformaldehyde in 0.12 M phosphate buffer) for at least 7 days and placed overnight in a sucrose solution (30% sucrose in 0.12 M phosphate buffered saline) for cryoprotection. Brains were cut and stained using Cresyl Violet to assess placement of the cannulas.

RESULTS

All animals were trained using three different numbers of distractors and three durations of motion to assess different demands on attention. Both factors influenced performance equally, with an increase in number of distractors or in duration of motion leading to a decrease in performance (Fig. 2). After injection of vehicle and when averaging over all durations of motion the animals performed at 59.3% (SD: ± 6.6), 49.6% (SD: ± 7.0), 42.9% (SD: ± 9.4), for 2, 5, 11 distractors respectively. When averaging over all num-

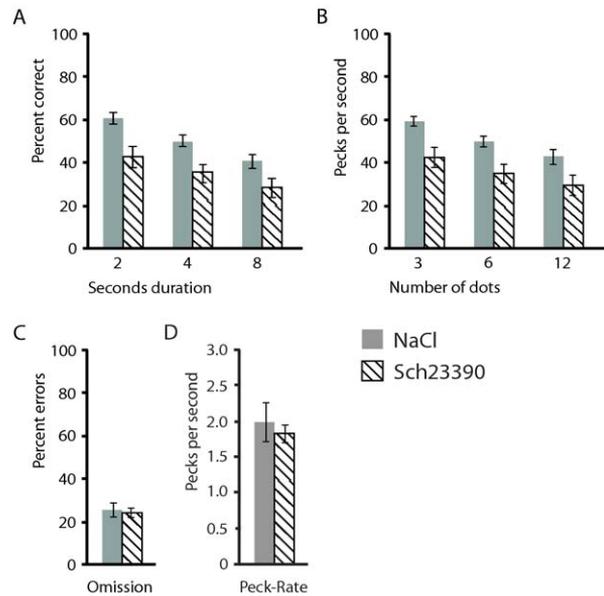


Fig. 2. The performance following injections of saline (grey bars) or Sch23390 (hatched bars). (A) The bars represent performance on trials with 2, 4 and 8 s motion duration, averaged over all numbers of dots. (B) The bars represent performance on trials with a total of 3, 6 and 12 moving dots, averaged over all durations of motion. (C) Bars represent the percentage of errors caused by response-omission. (D) The response rate while tracking the target during the motion-period.

bers of distractors, the animals performed at 60.9% (SD: ± 7.4), 50.4% (SD: ± 7.6), 40.6% (SD: ± 9.0), for 2, 4, 8 s of duration respectively. After injection of D1-antagonist, performance dropped on all conditions. When averaging over all durations of motion, the animals performed at 42.6% (SD: ± 54.9), 35.4% (SD: ± 4.7), 32.6% (SD: ± 4.8), for 2, 5, 11 distractors respectively. When averaging over all numbers of distractors, the animals performed at 42.9% (SD: ± 4.9), 38.1% (SD: ± 4.7), 29.2% (SD: ± 4.8), for 2, 4, 8 s of duration respectively.

The chance-level for these numbers is not trivial to calculate since it depends on the number of distractors and the duration of motion. A rough estimate, however, can be achieved by assuming equal probability for each dot. When averaging over all durations of motion, this approach would result in a chance-level of 33.3%, 16.7%, and 8.3% for 2, 5, and 11 distractors respectively. When averaging over all numbers of distractors, it would result in a chance-level of 19.4%. Note, however, that this is only a rough estimate. Duration of motion and screen position can also influence chance-level, since motion of the target always starts in the center of the screen and the target is more likely to appear close to the center after short durations of motion than after longer durations of motion. Therefore, equal probability cannot always be assumed for each dot irrespective of screen-position and the given numbers are to be understood as a rough estimate.

For behavioral analysis all values were averaged over the five injections for each animal and for each condition (vehicle, D1-antagonist). In four animals only four injections could be used for averaging since one injection each

had to be excluded due to problems with the injection. All statistics was performed on these averaged data. Statistical analysis was performed in Matlab using three-way ANOVA. Analysis revealed significant main effects for the number of distractors ($F(2,7)=17.6$, $P<0.001$), the duration of motion ($F(2,7)=23.9$, $P<0.001$) and the type of injection ($F(1,7)=55.2$, $P<0.001$) but no interaction between any of these factors. Injection of D1-antagonist lead to an overall reduction of performance of 15.1% compared to control-injections.

The animals solved the task by spontaneously pecking at the target during motion. This behavior gave us a measure to control for disturbance of motivation and motor-performance. After control-injections, the animals followed the target-dot at a peck-rate of 2.0 (SD: 0.13) pecks per second, after injections of D1-antagonist at a rate of 1.8 (SD: 0.26). A comparison of pecking-rate between these conditions using a paired *t*-test did not reveal a significant difference ($t(7)=1.5$, $P=0.17$). As an additional measure we assessed error-types. The percentage of errors caused by response-omission was 26.1% (SD: 3.3%) for control-injections and 24.8% (SD: 2.2%) for injections of D1-antagonist. These values were not found to be significantly different ($t(7)=0.4$, $P=0.70$) using a paired *t*-test. Microscopic analysis of the stained brain-sections confirmed that all cannulas were placed within the boundaries of the NCL as defined by Kröner and Güntürkün (1999).

DISCUSSION

In mammals, dopamine is implicated in neurological disorders associated with attentional dysfunction and numerous studies implicate prefrontal dopamine in the maintenance and protection of working memory. Yet little is known on the role of dopamine in attentional processes. To investigate this role we developed a novel attention-task, reminiscent of the shell game. In this task we manipulate two dimensions of attention, the number of distractors and the duration over which attention needs to be maintained. Our subjects showed a continuous reduction of performance with increasing number of distractors or with increasing task-duration. This drop in performance is indicative of an increased demand on attention and is in line with similar results obtained in humans when manipulating only number of distractors (Treisman and Gelade, 1980) or only task-duration (Manly et al., 1999). To investigate the contribution of dopamine to these dimensions of attention, we injected a D1-antagonist to the NCL of pigeons. We found that antagonist-injections cause a significant drop in performance compared to control-injections. This drop affects both manipulations, the number of distractors and the duration of motion, equally. To control if our results are based on altered motivational effects or on altered motor-performance we analyzed error-types and the peck-rate during motion. Both measures were unaffected by the injection and we therefore rule these alternative explanations out.

Our finding that delivery of D1-antagonist to the NCL exerts equal influence on both manipulations, number of distractors and duration of motion, indicates that the con-

tribution of dopamine to attention processes in the avian brain is twofold. It is involved in the selection of a target for attention as much as in the maintenance of attention to the target. While mammalian and avian brains are evolutionary highly separated, convergent evolution has led to a number of functional analogies in addition to the inherited homologies. It is generally accepted that, in spite of considerable structural differences, NCL and PFC are functionally comparable (Güntürkün, 2005a; Kirsch et al., 2008) and that the avian and mammalian dopaminergic systems are largely similar (Durstewitz et al., 1998; Güntürkün, 2005b). Therefore, we discuss our results in the light of mammalian literature on prefrontal dopamine.

A great number of studies investigated the role of prefrontal dopamine in working memory and our results are in line with the prevailing views. Modern models describe the role of dopamine in working memory in terms such as “gating mechanism” (Braver and Cohen, 2000; Cohen et al., 2002; Postle, 2005), a mechanism for the “protection against interference” (Durstewitz et al., 1999, 2000) and the “control of attention within working memory” (Seamans and Yang, 2004). Importantly, all these models stress the executive role of the PFC within working memory. The PFC is crucial for the protection and control of working memory rather than a specialized structure for the maintenance of sensory content for which it can recruit other, sensory, structures. There is ample evidence for this view. Neural activity observed in PFC during the delay-period of a working memory task (delay activity) has long been interpreted as a neural substrate of working memory (Fuster and Alexander, 1971). To date, delay activity has been observed in many pallial areas but activity recorded in the PFC differs in one important aspect. Only prefrontal delay-activity is stable over interfering sensory stimulation and is therefore capable of stabilizing working memory against interference (Miller et al., 1993, 1996). Similar results have been obtained using fMRI in humans. Postle (2005) could show that an increase in distraction during the delay-period leads to an increase in prefrontal but not in other task-related cortical activation. The NCL appears to have the same function as the PFC, the executive control of behavior (Güntürkün, 2005a; Kirsch et al., 2008). Such a controlling influence on working memory was recently demonstrated using single cell recordings in NCL. Here the authors could show that delay activity correlates with the decision to actively maintain or to forget information (Rose and Colombo, 2005).

The role of the PFC and of prefrontal dopamine in working memory might give important insight to its role in attention. In a recent review, Awh and Jonides (2001) provide a detailed discussion on the relationship between selective attention and working memory. The authors conclude that the underlying networks largely overlap and that information is held in working memory by the recruitment of mechanisms for spatial selective attention. The idea of this model is that the PFC selects targets for attention, thereby engaging specialized cortical areas in rehearsal of sensory

content. Evidence for this view was provided by several distinct approaches. In human subjects, EEG (Awh et al., 2000) and fMRI (Postle, 2005, 2006) were used to show that the networks for attention and working memory are virtually identical. Lebedev et al. (2004) trained monkeys on a task allowing to dissociate spatial attention from spatial working memory. When recording from single neurons under this task, they found that prefrontal delay activity correlates with attention to stimulus locations rather than the maintenance of stimulus locations. Using intracranial injections of D1-agonist to the PFC of rats, Chudasama and Robbins (2004) showed that attention as well as working memory are modulated by dopamine and can even benefit from increased levels of D1-receptor occupancy.

Here we show that injections of D1-antagonist to the NCL of pigeons disrupt the selection and maintenance of stimuli for attention when no working memory is required. This finding bridges an empirical gap between models of attention and models of dopamine in working memory. Our data provides evidence that dopamine serves a similar function in both scenarios. We argue that delay-activity along with its dopaminergic modulation is a mechanism for selection and maintenance of attentional targets at the prefrontal level. However, in order to select or maintain actual sensory information this view still owes a mechanism to influence processing in sensory domains. Such a mechanism is provided by the biased-competition model (Desimone and Duncan, 1995; Miller, 1999). This model is rooted in selective visual attention, where groups of neurons processing different aspects of a visual scene compete for activation. The group of neurons with the highest level of activity dominates the competition and persists while the remaining groups are suppressed. An excitatory signal, originating in the PFC, could exploit this mechanism by biasing the activity of one group and thereby automatically causing the suppression of the remaining activity.

Taken together, this leaves us with a putative mechanism to explain our results. In the beginning of training, dopamine is released when an unexpected reward is encountered. With an increasing strength of the association between the target-stimulus and reward this activation is shifted to the target-stimulus (Schultz, 2007). At this stage, dopamine helps forming the stimulus-reward association (Rose et al., 2009; Tsai et al., 2009). When training is completed, the presentation of the target-stimulus triggers dopamine-release to the NCL. This causes a switch in network properties favoring the maintenance of the current network-state (the representation of the target) (Durstewitz et al., 1999). Maintaining this activity at the NCL-level allows to bias sensory/motor structures towards the representation of the target which in turn allows maintaining attention to this target. If, as in the present study, dopamine-function is impaired, this bias might be lost and attention left vulnerable to interference and temporal decay.

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APPENDIX

Supplementary data

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