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Behavioural Processes xxx (2005) xxx–xxx
BEHAVIOURAL PROCESSES
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Dopamine D1 activation shortens the duration of phases in stereotyped grooming sequences

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Received 29 April 2005; received in revised form 13 July 2005; accepted 13 September 2005

Abstract

Rats frequently emit grooming actions in a highly stereotyped, syntactic chain in which three distinct phases of facially directed forearm movements are sequentially emitted in a rule-governed pattern and followed by body-directed licking. The present study evaluated the effects of the full dopamine D1 agonist, SKF 81297, and the partial dopamine D1 agonist, SKF 38393, on the duration of individual phases of stereotyped grooming chains. We found that systemic administration of SKF 81297 significantly shortened grooming chain duration. An examination of the fine temporal structure of syntactic grooming chain actions showed that duration changes were correlated with decreased numbers of actions in phases I and IV of the chain. Phases II and III were not changed in duration, although there were some structural distortions introduced. The partial D1 agonist, SKF 38393, had no effect on duration or number of component actions in the grooming chain. Based on these results, we hypothesize that the timing of syntactic grooming phase transitions may involve a D1-mediated internal clock process that is altered by full D1 agonist activation. By this model, SKF 81297 increases the speed of the clock used for the temporal control of grooming actions, and thus shortens phase durations.

Keywords: Dopamine receptors; Rats; Internal clock; Timing; Sequencing

1. Introduction

All behavior occurs in time. But what neural process controls when or how long each behavior is emitted? One hypothesis that has been proposed is that internal neurobiological clocks control the speed, timing and/or duration of behaviors. The simplest clock-behavior relation is seen in cases of circadian rhythmic behaviors, such as the 24 h sleep-wake cycle (Richter, 1967), produced by an endogenous oscillator centered in the suprachiasmatic nucleus (Ralph et al., 1990). While simple oscillators are good for producing rhythmic activity with low temporal variability, pure oscillation is relatively inflexible to perturbation, leading to effects such as jet lag. Furthermore, endogenous oscillators alone may not suffice for non-rhythmic, but temporally predictable situations (Kacelnik and Bateson, 1996). For complex temporal behaviors, animals may utilize a separate "interval timer", which can be started, stopped, and reset at arbitrary times (Brunner et al., 1992; Hinton and Meck, 1997).

Mechanisms similar to interval timers may also be needed for controlling the fine temporal structure of some instinctive movements such as fixed action patterns. The present study sought to examine the detailed temporal structure of a highly stereotyped fixed action pattern that occurs in rodent grooming, called a syntactic grooming chain, and to investigate the pharmacological mechanisms through which this temporal structure is modulated. This self-grooming sequence in rodents has been used in neuroethological studies as a model system of the neural control of sequential organization. The chain can be described as following syntactical rules, akin to the grammar of language (Berridge et al., 1987; Lieberman, 2000). The grooming sequence in rats is comprised of approximately 15–25 individual motor behaviors combined into four phases to form one syntactic chain pattern. Fig. 1 shows the four phases of grooming behavior as they unfold over time. Phase I is composed of 4–9 small amplitude, rapid (∼6 Hz), elliptical strokes directed around the nose and mouth with both paws, and lasts for about 1 s. Phase II is composed of 1–2 unilateral strokes of increasing amplitude and occurs for less than 1 s. Phase III typically lasts approximately 1–3 s, and

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0376-6357/$ – see front matter © 2005 Published by Elsevier B.V.
doi:10.1016/j.beproc.2005.09.008

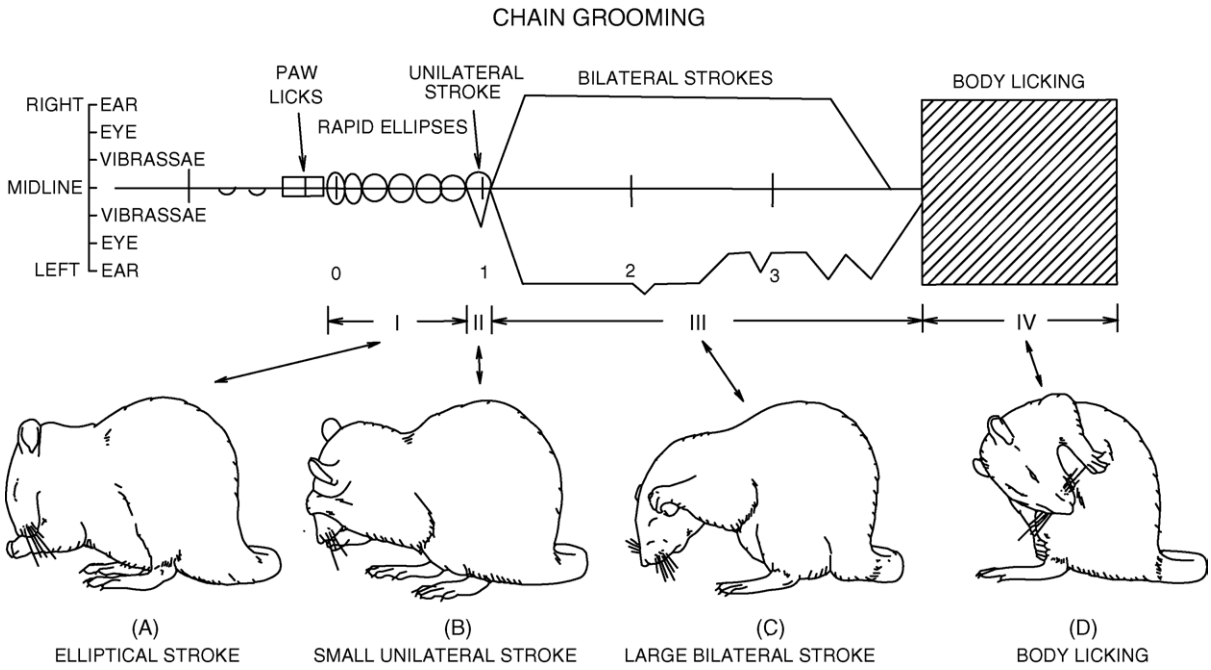

Fig. 1. Graphic illustration and choreographic diagram of the syntactic grooming chain. The upper portion of the figure is a choreographic diagram showing the amplitude and time course of the individual movements from a representative grooming chain. The lower portion of the figure is a graphic illustration of the whole body posture and respective phases of the grooming chain.

is comprised of 1–3 large, bilateral strokes. Finally, phase IV consists of a postural turn and licking directed at the torso, and usually continues for a minimum of several seconds. A digital video of the stereotyped grooming chain is available on the Behavioral Processes website (Supplementary Movie 1). Once the grooming chain is initiated (i.e., rapid, repeated phase I ellipses commence), the remaining chain components follow in the highly specific sequence described above with a probability that is 13,000 times greater than would be expected based upon each actions' individual probability of occurrence alone (Berridge et al., 1987).

What controls the temporal features of this fixed action pattern? A potential role for a timer or stroke counting mechanism is suggested by the existence of recursive within-phase action repetitions. For example, phase I contains 5–7 ellipse stroke actions repeated before the pattern moves on to phase II. Similarly, phase III contains several repetitions of bilateral stroke actions over the eyes, before the transition to phase IV. What process integrates the duration or reiteration of actions within phases to determine the proper moment for transition to the next phase? Given the repetitive nature of within-phase actions in the syntactic grooming chain, we propose that a temporal or numeric accumulation mechanism may be contained within dopamine-related brain circuits to produce the normative temporal structure of a syntactic grooming chain. This stereotyped behavior may provide a useful opportunity to study neural mechanisms of temporal regulation for an instinctive behavior.

While the individual behaviors composing the grooming chain are likely generated within the hindbrain (Berridge, 1989a), the sequential coordination of syntactic chains depends on dopamine neurotransmission in basal ganglia circuits, as the pattern is disrupted by dopaminergic nigrostriatal lesions (Berridge, 1989b), and the pattern is made more rigid by the transgenic elevation of neostriatal extracellular dopamine (Berridge et al., 2005). Dopamine's involvement in stereotypic chain grooming appears to require activation of the dopamine D1 receptor. For instance, D1, but not D2, receptors agonists have been shown to increase intense grooming, i.e., vigorous grooming directed toward the head followed by flank licking (Murray and Waddington, 1989). Furthermore, stereotyped chain grooming is disrupted following the transgenic loss of D1 receptors (Cromwell et al., 1998), while chain grooming is both increased and the pattern made more rigid by systemically (Berridge and Aldridge, 2000a) or centrally (Berridge and Aldridge, 2000b) administered D1 agonists.

Dopaminergic mechanisms have also been shown to play a role in modulating non-stereotypic, learned behaviors. For instance, dopamine has been proposed to encode deviations from reward expectation (Schultz and Dickinson, 2000), reflect the incentive salience of reward predicting cues (Berridge, 2001; Robinson and Berridge, 1993; Wyvell and Berridge, 2000), and promote the transition from cognitively mediated to automatic, habitual behavior (Everitt et al., 2001). Of particular relevance to the present experiment, dopamine has also been shown to modulate the timing of learned behaviors in operant tasks. Specifically, dopamingeric agonists such amphetamine (Abner et al., 2001; Chiang et al., 2000; Eckerman et al., 1987; Goldstone and Kirkham, 1968), methamphetamine (Buhusi and Meck, 2002; Cevik, 2003; Maricq et al., 1981; Meck, 1983), and cocaine (Matell et al., 2004) cause temporally guided responding to occur earlier in time, while dopaminergic antagonists, such as haloperidol (Drew et al., 2003; Maricq and Church, 1983; Meck,

1983, 1986) cause responding to occur later. The magnitude of these dopamine-induced shifts in response time is proportional to the duration being timed, suggesting an effect on a central timekeeper (Drew et al., 2003; Meck, 1983, 1986).

We combined these themes to investigate whether dopamine modulates the temporal patterning of stereotypic sequential grooming. The present study addresses this issue by analyzing the number, duration, and speed of grooming chain movements and phases, and the effects of dopamine D1 agonists on these measures (we did not use a D2 agonist because of previous findings that D2 agonists dramatically reduce emission of syntactic chains; Berridge and Aldridge, 2000a). Two D1 agonists were used, the partial D1 agonist, SKF 38393 (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine) and the full D1 agonist, SKF 81297 (6-chloro-2,3,4,5-tetrahydro-7,8-dihydroxy-1-pheyl-1H-3-benzazepine). Both of these agonists are highly selective for the D1 dopamine receptor, with both SKF 38393 and SKF 81297 showing ∼500 times greater affinity for the D1 receptor over the D2 receptor in vitro (Andersen and Jansen, 1990). Both stimulate adenylate cyclase (Kebabian and Calne, 1979), although the partial agonist, SKF 38393 does so at only 45% of the intrinsic level of dopamine, whereas SKF 81297 stimulates adenylate cyclase at 88% of that of dopamine in in vitro evaluations (Andersen and Jansen, 1990). We report here that the full dopamine D1 agonist, SKF 81297, but not the partial D1 agonist, SKF 38393, shortens the duration of the stereotyped grooming chain.

2. Materials and methods

2.1. Subjects

Ten male Fisher 344BNF1 rats, 6 months of age, were used for these experiments. Rats were housed with a 12:12 reverse light–dark cycle. Testing was done during the animals' most active period (i.e., the first few hours of darkness). Video recordings were done in a darkened environment with dim (25 W) red lights, to minimize disruption to the circadian periodicity.

2.2. Grooming recording

Animals were placed in a rectangular chamber over a clear glass floor and videotaped from below. Close-up views of the head through the bottom of the recording chamber were reflected into a videocamera by a mirror at a 45° angle to allow the trajectory of both forepaw movements to be seen clearly. Experience indicated that this bottom view is best for observing grooming behavior. Animals were allowed to freely move within the recording chamber, and grooming behaviors were spontaneous. All behavior was videotaped for 1 h in each condition. Prior to drug administration, animals were handled for 3 days and acclimated to the recording chamber.

2.3. Drug administration

The partial D1 agonist (SKF 38393, Sigma, USA) and the full D1 agonist (SKF 81297, Sigma, USA) were dissolved in a vehicle of 0.9% saline. Each day of drug administration (Tuesday and Thursday), rats were given subcutaneous injections of vehicle and videotaped for 1 h. They were removed from the recording chamber, given a subcutaneous injection of either SKF 38393 or SKF 81297 and returned to the recording chamber for an additional hour of videotaping. Each rat received a total of three doses of each of the two drugs. The drug administered on each test day was chosen randomly, whereas the dose within each drug increased on subsequent sessions. For SKF 38393, all rats received the following three doses: 1.0, 3.0, 10.0 mg/kg. For SKF 81297, due to a decision to increase the relative separation of drug doses partway through the experiment, four rats received the following doses (0.40, 0.80, 1.00 mg/kg), while the other six rats received the following doses (0.20, 0.40, 1.00 mg/kg).

2.4. Grooming sequence analysis

Behavioral analyses consisted of computer assisted, frame-by-frame video scoring (Berridge, 1990) to assess onset times of each action and phase. Computer transcription of the onset times of individual grooming actions and/or phases was achieved by assessment of the location of the forepaws in relation to the head (phases I–III), or relation of the head to the body (phase IV) according to the following rules. Phase I onset began at the moment the forepaws touched the side of the snout around the vibrissae just prior to the rat initiating rapid (6 Hz), small amplitude, bilaterally symmetrical forepaw movements. Phase II onset began upon separation of the paws indicating an asymmetry in the amplitude of the two forepaws. As the phase of the forepaws became asynchronous, the amplitude of the hand's trajectory increased. Phase III commenced upon a return to bilateral, symmetrical forepaw movement, which co-occurred with the largest amplitude trajectories, such that the hands frequently touched the head behind the ears. Finally, phase IV began with the turn of the head and was followed by flank licking on one side of the torso. This flank licking moved in a rostral to caudal direction before the rat either ended flank licking abruptly, began licking in a caudal to rostral direction, or crossed the midline to continue flank licking on the other side of the body. The onset of a grooming action was extracted with the accuracy of a single video frame, i.e. 33 ms. Grooming events were catalogued according to the particular action or stroke and as a complete chain (all four phases in order without disruption), an imperfect chain (all four phases, but out of order or with additional strokes inserted) (e.g., paw licking), an incomplete chain (chain is initiated with elliptical strokes, but does not continue through to phase IV flank licking) or non-chain grooming. These behaviors and their associated times were analyzed offline using standard database software (Paradox). For the present study, only syntactically complete chains were assessed for changes in duration. This focus on complete patterns avoided potential confounds between sequential status and temporal features. For example, slower phase I ellipse duration is associated with lower sequential completion of later phases (Berridge, 1990).

Chain duration was initially measured from phase I onset through the end of phase IV (as defined by the termination of flank licking or by crossing of the midline following flank lick-

ing on one side, whichever came first). Following assessment of overall chain duration effects, grooming behavior under the highest dose of SKF 81927 (1.0 mg/kg) was re-examined in more detail to determine the duration of each individual movement for nine rats which had sufficient video data available. We quantified the phase duration and the number of forelimb face strokes for phases I–III. In order to evaluate whether changes in the duration of phase IV were associated with changes in the speed of licking movements or changes in the total number of licking movements, we quantified the number of licks (in the 86% of chains in which all lick movements were visible). In addition, to minimize the variance in the duration and lick counts of phase IV, chain completion was defined as the point in time at which the rat (a) reversed the direction of flank licking and began licking the body in a rostral direction, or (b) crossed the midline, or (c) terminated flank licking (whichever came first). These latter two behaviors (midline crossing or termination) invariably occurred when the rat reached the caudal end of its body, and therefore we used this feature as the defining endpoint. For expository purposes, detailed choreographic information was further analyzed from a representative grooming chain of both the vehicle and drug session in order to characterize moment-to-moment trajectories of the forepaws in relation to the face.

All video scoring was performed by trained observers who were blind to the drug condition and hypotheses. Inter-observer agreement was evaluated by a comparison of the video frame/time stamp in which phase I elliptical strokes were judged to be initiated during the initial chain sequence analysis and the more detailed stroke by stroke analysis. Likewise we compared the timestamp associated with onset of phase IV flank licking in the stroke by stroke analysis with that from the flank lick count analysis. Different observers conducted the three different analyses. Out of 488 grooming events in 244 chains, 396 observations (81%) were in perfect agreement. The remaining 19% of the observations were typically offset by a single frame (median of the offsets = .033 s). The correlation between durations of different observers' assessment of the same chains was 0.94. As all observer's were blind to the hypotheses being evaluated, and as the same observer scored both the vehicle and drug data for each subject, any individual bias regarding the precise moment of phase changes would not be expected to impact the analyses.

2.5. Statistical analyses

Chain grooming occurs at relatively low rates in naïve animals, such that some vehicle sessions provided no grooming data. To avoid discarding the subsequent drug data in a repeated measures design, all vehicle data were pooled for chain duration comparisons. To facilitate a balanced repeated-measures statistical design, we classified the doses that each rat received as low, medium, and high for each drug. Statistical evaluations comparing the duration of the chain on vehicle versus drug were performed using a repeated measure ANOVA with drug (SKF 38393, SKF 81297) and dose (vehicle, low, medium, high) as factors. One rat did not perform any grooming on the medium dose of SKF 38393, and this data point was replaced with the average of this subject's other data. To more specifically analyze the dose-dependency of the drugs, planned comparisons between vehicle and drug dose were performed with a paired-samples *t*-test, using the actual doses received by each rat, rather than the relative dose. All analyses were evaluated at a criterion of $p < .05$.

3. Results

SKF 81297, a full dopamine D1 agonist, produced a dose-dependent decrease in the duration of the syntactic grooming chain (Fig. 2). A significant effect was found for both drug [$F(1,9) = 5.669$, $p < .05$] and dose [$F(3,27) = 4.291$, $p < .05$]. The drug × dose interaction was not significant [$F(3,27) = 1.083$, $p > .10$]. These effects were due to SKF 81297, as a repeated measures ANOVA run on these data alone revealed a significant effect of dose [$F(3,27) = 5.817$, $p < .005$], whereas the same analysis was not significant for SKF 38393 [$F(3,27) = 1.708$, $p > .10$]. Planned comparisons of vehicle to each dose of SKF 81297 revealed an effect that was roughly linear with dose [0.2 mg/kg, $t(5) = 1.582$, $p > .10$; 0.4 mg/kg, $t(9) = 1.874$, $p < .10$; 0.8 mg/kg, $t(3) = 2.679$, $p < .10$; 1.0 mg/kg, $t(9) = 4.104$, $p < .001$]. The apparent linearity in effect size with increasing dose of SKF 81297 was tested and verified using a polynomial contrast [$p < .01$]. In contrast, planned comparisons evaluating vehicle to each dose of SKF 38393 revealed a significant effect only for the lowest dose [1.0 mg/kg, $t(9) = 3.273$, $p < .05$; 3.0 mg/kg, $t(8) = -.0.076$, $p > .10$; 10.0 mg/kg, $t(9) = .1.319$, $p > .10$]. Furthermore, the polynomial contrast revealed no linearity to the dose effect [$p > .10$].

A detailed analysis was performed on phase duration, stroke counts and stroke duration for the highest dose of SKF 81297 versus the vehicle session immediately preceding that drug/dose testing session. Fig. 3A shows the effects of 1.0 mg/kg SKF 81297 on the absolute duration of each phase, whereas Fig. 3B plots the same data in proportional terms.

Phases I and IV both showed decreases in duration with SKF 81297 dopamine D1 activation. A repeated measures ANOVA with drug (vehicle, SKF 81297) and phase (I–IV) as

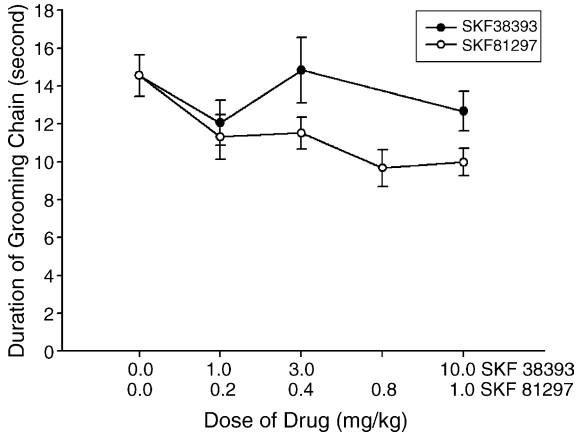

Fig. 2. Duration of the entire grooming chain as a function of drug and dose. Error bars are standard errors of the mean.

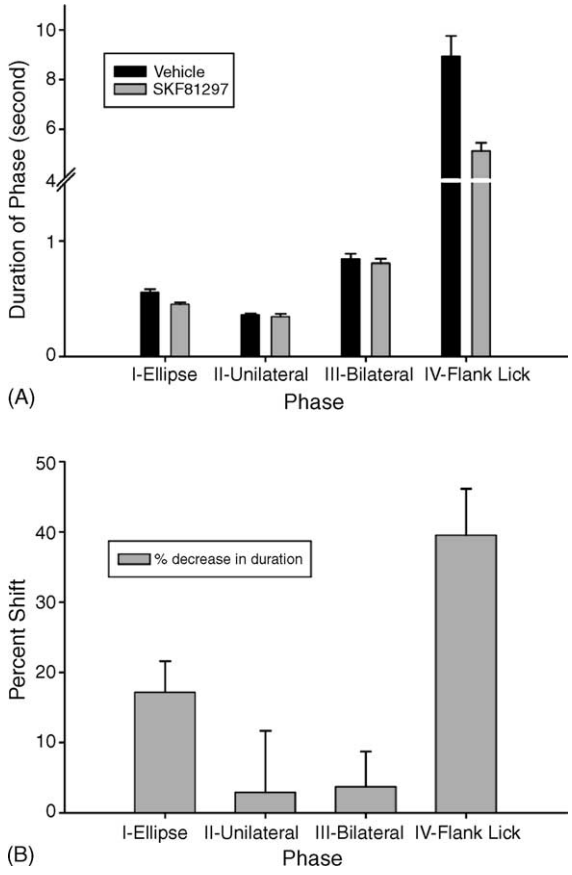

Fig. 3. Duration (A) and proportional shortening (B) of individual phases of the syntactic grooming chain following administration of vehicle and the highest dose (1.0 mg/kg) of SKF 81297. Error bars are standard errors of the mean. The ordinate is "broken" to prevent masking the shortening of phase I.

factors demonstrated a significant effect of drug [$F(1,8) = 28.1$, $p < .001$], phase [$F(3,24) = 164.0$, $p < .001$], and a drug × phase interaction [$F(3,24) = 24.4$, $p < .001$]. Planned comparisons showed significantly decreased durations of phase I [$t(8) = 3.22$, $p < .05$], and phase IV [$t(8) = 5.04$, $p < .001$] after SKF 81297.

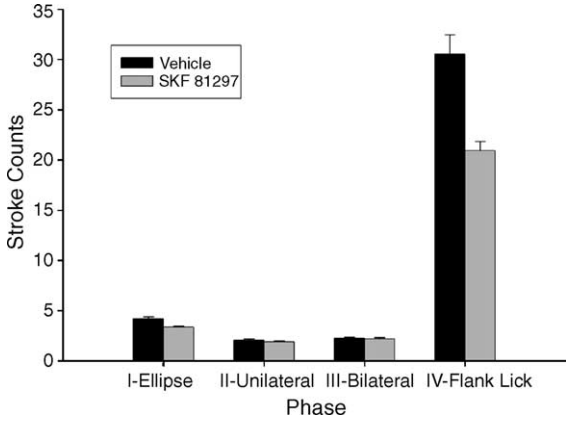

Fig. 5. Stroke counts of individual phases of the syntactic grooming chain following administration of vehicle and the highest does (1.0 mg/kg) of SKF 81297. Error bars are standard errors of the mean.

Phases II and III, in contrast, revealed no significant duration change; however, close visual inspection suggested that during drug treatment there was some increased blending between phases II and III. This blending was evident as a mixture of the strokes from the two phases, such that both arms moved upward across the face like bilateral, phase III strokes, but with one arm held much lower like unilateral phase II strokes (Fig. 4).

To test whether the change in duration was due to a change in stroke duration or number, we counted strokes for each phase (Fig. 5) and determined the average individual stroke duration. Like individual phase durations, a repeated measures ANOVA (drug, phase) comparing individual phase counts from vehicle to drug demonstrated a significant effect of SKF 81297 [$F(1,8) = 27.4$, $p < .001$], phase [$F(3,24) = 387.7.0$, $p < .001$], and a drug × phase interaction [$F(3,24) = 21.8$, $p < .001$]. In phases I and IV, which were the phases that were significantly shorter in duration, the numbers of strokes or licks were also significantly decreased (planned comparisons following 1.0 mg/kg SKF 81297 [phase I, $t(8) = 3.56$, $p < .01$; phase IV, $t(8) = 2.31$, $p < .005$]). No significant changes were seen for stroke number in

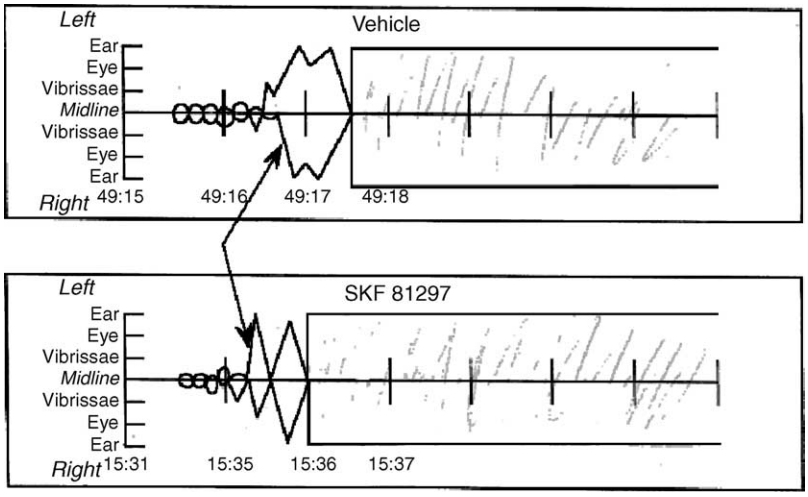

Fig. 4. Choreographic diagram of a representative grooming chain following administration of vehicle (top) and SKF 81297 (bottom). Notice the decreased number of phase I ellipses in the drug condition as compared to the vehicle condition. Also note the "phase blending" between phases II and III, in which the bilateral strokes are of asymmetric amplitude, as indicated by the arrows.

phases II and III, nor were significant changes in stroke duration observed in any phase.

In order to investigate whether there is a common source of duration modulation within the grooming chain, we assessed the degree to which the durations of each phase of the grooming chain were correlated. A positive correlation between the durations of phases I and IV was found for every rat ($r = 0.10–0.70$, average = 0.44) during the vehicle sessions. A sign test showed this number of positive correlations (9/9) to be significant ($p < .005$). In contrast, negative correlations were usually found (8/9) between phases II and III under vehicle ($r = -0.81–0.26$, average = −0.36, $p < .05$). No significant correlations were found for any other phase relations or any comparison under drug.

4. Discussion

The current results demonstrate that the administration of the full dopamine D1 agonist, SKF 81297, but not the partial dopamine D1 agonist, SKF 38393, decreased the duration of a fixed action pattern, the highly stereotyped syntactic grooming chain in rats, by shortening phases within it. The shortening of phases was coincident with a reduced number of component actions within phases I and IV of the fixed action pattern (reduced number of ellipse strokes and licks). In contrast, no change in stroke duration was observed. These data demonstrate that full stimulation of the dopamine D1 receptor can potentiate the rate of transition through a stereotyped behavioral pattern. However, the mechanism through which dopamine facilitates this chain shortening is not immediately clear.

What source of information is used to trigger phase transitions that could be modulated by dopamine? One simple possibility is that phase transitions occur probabilistically, and that dopamine raises the probability of these transitions, thereby shortening the duration of each phase. However, if phase transitions were simply probabilistic in nature, the number of stroke counts in each phase would be geometrically distributed, a result which is not seen. Another possibility is that a stimulus–response chain resulting from sensory feedback is used to make the transition decision, and that dopamine modulates this sensory feedback. However, deafferentation of the trigeminal nerve to remove facial somatosensory feedback does not alter the sequence or amplitude of stereotyped syntactic grooming strokes (Berridge and Fentress, 1986), strongly suggesting that sensory feedback is not ordinarily needed to decide when to make transitions between phases of the pattern, and so is unlikely to be the chief mechanism involved here. A third, related possibility is that stimulation of the dopamine D1 receptor induces a peripheral change, such as a decrease in salivation, which might diminish the ability of the rat to continue certain grooming actions, such as flank licking. However, several pieces of evidence argue against such a possibility. First, we observed a decrease in the duration of phase I as well as phase IV, in which rapid forepaw strokes, although oriented near the mouth, are not licked, suggesting decreased salivation could not play the only role. Second, while the aforementioned trigeminal nerve cuts (Berridge and Fentress, 1986) do not alter salivation directly, the feedback signals from the mucous membranes are eliminated. As this feedback manipulation had no effect on stereotypic chain grooming, it is suggestive that direct alterations in salivation would be unlikely to alter grooming duration. Finally, dopamine stimulates, rather than attenuates salivation (Iwabuchi et al., 1987).

A more likely scenario is that either the number of movements in each phase, or the duration of movements in each phase, is tabulated directly by a mechanism involving dopamine neurotransmission. The present findings are similar to previous work investigating the neural basis of temporal perception and control, which has shown that dopaminergic agents can modulate the speed of an internal clock utilized for timing both learned behaviors, such as operant responding (Buhusi and Meck, 2002; Maricq and Church, 1983; Maricq et al., 1981; Matell et al., 2004; Meck, 1983, 1986) as well as unlearned behaviors, such as the speed of licking during drinking (Badiani and Stewart, 1999). In information-processing models of these temporally controlled behaviors, a time-varying neural signal is produced that can be started, stopped, reset, and compared to previously stored signal values in order to control behavior. Within this framework, dopaminergic agonists positively modulate or increase the rate of change in the time-varying signal, thereby allowing the current clock signal to match previously stored clock signals earlier in real time. Importantly, the interpretation that dopaminergic drugs modulate clock speed rather than latency to start the clock hinges on the fact that the magnitude of the drug-induced shift is proportional to the signal duration being timed (Meck, 1983).

In the present context, this time varying clock signal would be used to trigger phase transitions in the grooming chain. In one instantiation of a phase transition timer, the clock would be started upon chain initiation, and each subsequent phase would be initiated once the signal reached the appropriate value. In this scenario, stimulation of the dopamine D1 receptor would increase the rate of change of the clock signal, thereby causing each phase to be initiated earlier than normal, and thereby decreasing the duration of each phase in a proportional manner (e.g., all phase durations are reduced by 20%). However, in contrast to the proportional drug effects seen in operant tasks, the decreases in the duration of each phase following administration of SKF 81297 were not proportional, decreasing by 17%, 3%, 4%, and 40% respectively (Fig. 3B). While this non-proportionality may be due to separate clocks being utilized for each grooming phase with each susceptible to differing degrees of dopaminergic modulation, the differential phase shortening may simply reflect “floor effects” due to different numbers of component strokes. Specifically, if phase transitions do not regularly occur prior to stroke completion, phases with a small number of strokes (e.g., the two stroke behavior typically seen in phases II and III) would require at least a 50% reduction in duration (i.e., a 100% increase in clock speed) in order for an effect to be seen (i.e., a reduction from two strokes to one stroke). Likewise, the four strokes seen in phase I would drop by only one stroke, unless the clock speed increased by 100%. Indeed, as long as strokes must be completed prior to phase transitions, the obtained duration changes of all four phases are consistent with a uniform 40% decrease in duration induced by an 80%

increase in clock speed across all four phases. Thus, the current data are in line with a single dopaminergically modulated clock signal being used to control the durations of individual phases of the grooming chain. Consistent with this interpretation is the finding that the durations of phases I and IV in individual grooming chains were positively correlated in vehicle treated animals, strongly suggesting a common duration-modulating factor. Although it remains unclear whether dopamine plays the role of this duration modulating factor in vehicle-treated animals, the current results demonstrate its capacity for doing so.

Do the current data allow us to differentiate between action counting versus phase duration processing? Some support for the monitoring of phase duration, rather than stroke count, can be seen in Fig. 4, in which phases II and III appear to "blend", suggesting that a phase transition signal occurred prior to stroke completion. Such action blending would not be predicted to result from a mechanism that triggered early initiation of phase III simply because a decreased number of phase II actions were required. It contrast, phase blending is predicted to occur if the required clock value for initiating a phase transition was obtained during the execution of a stroke. Nonetheless, the weight of the evidence is consistent with D1 agonist induced distortion of either action timing or action counting processes. Indeed, the mechanisms underlying timing and counting may be intimately related. For instance, Meck and Church (1983) demonstrated that both learned timing and counting were modulated in an equivalent manner by dopamine agonist administration, and that both processes can be accounted for by the same pacemaker-accumulator model running in different accumulator "modes", with pacemaker pulses either released tonically at a high rate (timing) or released phasically (counting) upon occurrence of an event or action. Whatever the process underlying phase transitions, we suggest that these transitions are the focal point for dopamine's effects.

Several pieces of data point to the basal ganglia, and its dopaminergic input from the substantia nigra pars compacta as playing a key role in the production of non-chain grooming, stereotyped chain grooming, and other non-grooming, stereotyped behaviors. For instance, while centrally administered adrenocorticotropic hormone (ACTH) increases non-stereotyped grooming (Berridge and Aldridge, 2000b; Gispen et al., 1975), dopaminergic antagonists attenuate this grooming (Wiegant et al., 1977). Likewise, peripherally administered dopamine D1 agonists have been shown to increase non-stereotyped grooming (Berridge and Aldridge, 2000a; Deveney and Waddington, 1997; Molloy and Waddington, 1984), as well as more stereotypical "intense" grooming (Berridge and Aldridge, 2000a; Murray and Waddington, 1989). Similarly, centrally administered dopamine D1 agonists increase both non-stereotyped grooming as well as stereotyped grooming, whereas centrally administered ACTH does not alter stereotyped grooming (Berridge and Aldridge, 2000b). Activation of a variety of other stereotyped behavioral patterns have also been linked to dopaminergic stimulation in the striatum, such as focused stereotypes (Ellinwood and Balster, 1974; Kuczenski and Segal, 1999), oral stereotypes (Cho et al., 1999) and stereotypical locomotion (Fritts et al., 1997) in rats, "taffy-pulling" in mice (Chartoff et al., 2001), head swinging and repetitive postural shifting in squirrel monkeys (Saka et al., 2004), crib biting in horses (McBride and Hemmings, 2005), and drug-induced (Rylander, 1972) and psychiatric disorder related stereotypes, such as obsessive compulsive disorder (McDougle et al., 1993) and Tourette's syndrome (Diaz-Anzaldua et al., 2004) in humans. These same structures are also likely to be involved in the temporal control of stereotyped behavior. Combined cortical/striatal lesions led to a slight lengthening of chain grooming, without a change in stroke number or speed, whereas cortical lesions alone had no effect (Berridge and Whishaw, 1992). The same chain lengthening effects were seen following lesions restricted to the dorsolateral portion of the striatum (Cromwell and Berridge, 1996). Likewise, lesions of the ventral neostriatum or globus pallidus led to similar effect on phase duration, and in addition produced a slight slowing of phase I ellipses (Cromwell and Berridge, 1996).

The basal ganglia have also been shown to be important in operant timing procedures. Systemic dopamine manipulations (Buhusi and Meck, 2002; Maricq and Church, 1983; Maricq et al., 1981; Matell et al., 2004; Meck, 1983, 1996), and striatal electrophysiological recordings (Matell et al., 2003) in rats, and functional imaging work in humans (Nenadic et al., 2003; Rao et al., 2001) all provide support for a role of the basal ganglia in temporal perception. Dopamine has also been shown to increase response switching (Evenden and Robbins, 1983), impulsivity (Evenden and Ko, 2005; Evenden and Meyerson, 1999), and rate dependent responding (Odum et al., 2002) in operant tasks, behaviors which could contribute to dopamine-induced alterations in the temporal control of behavior, particularly if such temporal control is mediated by transitioning through a fixed behavioral sequence (Killeen and Fetterman, 1988; Machado, 1997). Interestingly, in contrast to the present results, D2, and not D1, antagonists have been shown to modulate operant timing (Drew et al., 2003; Meck, 1986). Unfortunately, previous work exploring the effects of D2 agonists on grooming have found that it potently decreases grooming and suppresses the occurrence of syntactic grooming chains (Berridge and Aldridge, 2000a), making it difficult to compare D2 receptor activation effects on syntactic grooming phase durations.

It may be noteworthy that the full D1 agonist modulated the grooming action clock/counter here, whereas the partial D1 agonist did not. In contrast, we have previously found that systemic administration of the partial agonist was most effective in promoting sequential super-stereotypy, which made the entire pattern more rigid as a whole, and more likely to be completed once started (Berridge and Aldridge, 2000a). A dissociation between sequential super-stereotypy and phase shortening for partial versus full D1 agonists might indicate that sequential features and temporal features of the fixed action pattern have slightly different relations to D1 processes. The relation of temporal versus sequential features of the pattern to receptor subtype activation may deserve further investigation. In addition, we suggest that future investigations of the similarities and differences in the mechanisms involved in timing instinctive versus learned, appetitively-motivated behavior may reveal important information regarding the role that timing and time perception plays in cognition and behavior.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.beproc.2005.09.008.

References

Abner, R.T., Edwards, T., Douglas, A., Brunner, D., 2001. Pharmacology of temporal cognition in two mouse strains. Int. J. Comparative Psychol. 14 (3–4), 189–210.

Andersen, P.H., Jansen, J.A., 1990. Dopamine receptor agonists: selectivity and dopamine D1 receptor efficacy. Eur. J. Pharmacol. 188 (6), 335–347.

Badiani, A., Stewart, J., 1999. Long-lasting sensitization to the accelerating effects of amphetamine on the speed of an internal clock. Behav. Brain Res. 100 (1–2), 217–223.

Berridge, K.C., 1989a. Progressive degradation of serial grooming chains by descending decerebration. Behav. Brain Res. 33 (3), 241–253.

Berridge, K.C., 1989b. Substantia nigra 6-OHDA lesions mimic striatopallidal disruption of syntactic grooming chains: a neural systems analysis of sequence control. Psychobiology 17, 377–385.

Berridge, K.C., 1990. Comparative fine structure of action: rules of form and sequence in the grooming patterns of six rodent species. Behaviour 113, 21–56.

Berridge, K.C., 2001. Reward learning: reinforcement, incentives, and expectations. In: Medin, D.L. (Ed.), The Psychology of Learning and Motivation: Advances in Research and Theory, vol. 40. Academic Press, San Diego, CA, pp. 223–278.

Berridge, K.C., Aldridge, J.W., 2000a. Super-stereotypy. I. Enhancement of a complex movement sequence by systemic dopamine D1 agonists. Synapse 37 (3), 194–204.

Berridge, K.C., Aldridge, J.W., 2000b. Super-stereotypy. II. Enhancement of a complex movement sequence by intraventricular dopamine D1 agonists. Synapse 37 (3), 205–215.

Berridge, K.C., Aldridge, J.W., Houchard, K.R., Zhuang, X., 2005. Sequential super-stereotypy of an instinctive fixed action pattern in hyperdopaminergic mutant mice: a model of obsessive compulsive disorder and Tourette's. BMC Biol. 3 (1), 4.

Berridge, K.C., Fentress, J.C., 1986. Contextual control of trigeminal sensorimotor function. J. Neurosci. 6 (2), 325–330.

Berridge, K.C., Fentress, J.C., Parr, H., 1987. Natural syntax rules control action sequence of rats. Behav. Brain Res. 23 (1), 59–68.

Berridge, K.C., Whishaw, I.Q., 1992. Cortex, striatum and cerebellum: control of serial order in a grooming sequence. Exp. Brain Res. 90 (2), 275–290.

Brunner, D., Kacelnik, A., Gibbon, J., 1992. Optimal foraging and timing processes in the starling *Sturnus vulgaris*: effect of intercapture interval. Anim. Behav. 44, 597–613.

Buhusi, C.V., Meck, W.H., 2002. Differential effects of methamphetamine and haloperidol on the control of an internal clock. Behav. Neurosci. 116 (2), 291–297.

Cevik, M.O., 2003. Effects of methamphetamine on duration discrimination. Behav. Neurosci. 117 (4), 774–784.

Chartoff, E.H., Marck, B.T., Matsumoto, A.M., Dorsa, D.M., Palmiter, R.D., 2001. Induction of stereotypy in dopamine-deficient mice requires striatal D1 receptor activation. Proc. Natl. Acad. Sci. U.S.A. 98 (18), 10451–10456.

Chiang, T.J., Al-Ruwaitea, A.S., Mobini, S., Ho, M.Y., Bradshaw, C.M., Szabadi, E., 2000. The effect of D-amphetamine on performance on two operant timing schedules. Psychopharmacology (Berl) 150 (2), 170–184.

Cho, A.K., Melega, W.P., Kuczenski, R., Segal, D.S., Schmitz, D.A., 1999. Caudate-putamen dopamine and stereotypy response profiles after intravenous and subcutaneous amphetamine. Synapse 31 (2), 125–133.

Cromwell, H.C., Berridge, K.C., 1996. Implementation of action sequences by a neostriatal site: a lesion mapping study of grooming syntax. J. Neurosci. 16 (10), 3444–3458.

Cromwell, H.C., Berridge, K.C., et al., 1998. Action sequencing is impaired in D1A-deficient mutant mice. Eur. J. Neurosci. 10 (7), 2426–2432.

Deveney, A.M., Waddington, J.L., 1997. Psychopharmacological distinction between novel full-efficacy "D1-like" dopamine receptor agonists. Pharmacol. Biochem. Behav. 58 (2), 551–558.

Diaz-Anzaldua, A., Joober, R., Riviere, J.B., Dion, Y., Lesperance, P., Richer, F., et al., 2004. Tourette syndrome and dopaminergic genes: a family-based association study in the French Canadian founder population. Mol. Psychiatry 9 (3), 272–277.

Drew, M.R., Fairhurst, S., Malapani, C., Horvitz, J.C., Balsam, P.D., 2003. Effects of dopamine antagonists on the timing of two intervals. Pharmacol. Biochem. Behav. 75 (1), 9–15.

Eckerman, D.A., Segbefia, D., Manning, S., Breese, G.S., 1987. Effects of methylphenidate and D-amphetamine on timing in the rat. Pharmacol. Biochem. Behav. 27 (3), 513–515.

Ellinwood Jr., E.H., Balster, R.L., 1974. Rating the behavioral effects of amphetamine. Eur. J. Pharmacol. 28 (1), 35–41.

Evenden, J., Ko, T., 2005. The psychopharmacology of impulsive behaviour in rats. VIII. Effects of amphetamine, methylphenidate, and other drugs on responding maintained by a fixed consecutive number avoidance schedule. Psychopharmacology (Berl) 180 (2), 294–305.

Evenden, J., Meyerson, B., 1999. The behavior of spontaneously hypertensive and Wistar Kyoto rats under a paced fixed consecutive number schedule of reinforcement. Pharmacol. Biochem. Behav. 63 (1), 71–82.

Evenden, J.L., Robbins, T.W., 1983. Increased response switching, perseveration and perseverative switching following D-amphetamine in the rat. Psychopharmacology (Berl) 80 (1), 67–73.

Everitt, B.J., Dickinson, A., Robbins, T.W., 2001. The neuropsychological basis of addictive behaviour. Brain. Res. Rev. 36 (2–3), 129–138.

Fritts, M.E., Mueller, K., Morris, L., 1997. Amphetamine-induced locomotor stereotypy in rats is reduced by a D1 but not a D2 antagonist. Pharmacol. Biochem. Behav. 58 (4), 1015–1019.

Gispen, W.H., Wiegant, V.M., Greven, H.M., de Wied, D., 1975. The induction of excessive grooming in the rat by intraventricular application of peptides derived from ACTH: structure–activity studies. Life Sci. 17 (4), 645–652.

Goldstone, S., Kirkham, J.E., 1968. The effects of secobarbital and dextroamphetamine upon time judgment: intersensory factors. Psychopharmacologia 13 (1), 64–73.

Hinton, S.C., Meck, W.H., 1997. The 'internal clocks' of circadian and interval timing. Endeavour 21 (1), 3–8.

Iwabuchi, Y., Aoki, C., Masuhara, T., 1987. Effects of dopamine on the secretion of glycoproteins from the functional segments of the rat submandibular gland. Jpn. J. Pharmacol. 45 (2), 149–158.

Kacelnik, A., Bateson, M., 1996. Risky theories: the effects of variance on foraging decisions. Am. Zool. 36, 402–434.

Kebabian, J.W., Calne, D.B., 1979. Multiple receptors for dopamine. Nature 277 (5692), 93–96.

Killeen, P.R., Fetterman, J.G., 1988. A behavioral theory of timing. Psychol. Rev. 95 (2), 274–295.

Kuczenski, R., Segal, D.S., 1999. Sensitization of amphetamine-induced stereotyped behaviors during the acute response. J. Pharmacol. Exp. Ther. 288 (2), 699–709.

Lieberman, P., 2000. Human Language and Our Reptilian Brain: The Subcortical Bases of Speech, Syntax, and Thought. Harvard University Press, Cambridge, MA.

Machado, A., 1997. Learning the temporal dynamics of behavior. Psychol. Rev. 104 (2), 241–265.

Maricq, A.V., Church, R.M., 1983. The differential effects of haloperidol and methamphetamine on time estimation in the rat. Psychopharmacology 79 (1), 10–15.

Maricq, A.V., Roberts, S., Church, R.M., 1981. Methamphetamine and time estimation. J. Exp. Psychol.: Anim. Behav. Process. 7 (1), 18–30.

Matell, M.S., King, G.R., Meck, W.H., 2004. Differential modulation of clock speed by the administration of intermittent versus continuous cocaine. Behav. Neurosci. 118 (1), 150–156.

Matell, M.S., Meck, W.H., Nicolelis, M.A., 2003. Interval timing and the encoding of signal duration by ensembles of cortical and striatal neurons. Behav. Neurosci. 117 (4), 760–773.

McBride, S.D., Hemmings, A., 2005. Altered mesoaccumbens and nigrostriatal dopamine physiology is associated with stereotypy development in a non-rodent species. Behav. Brain. Res. 159 (1), 113–118.

McDougle, C.J., Goodman, W.K., Price, L.H., 1993. The pharmacotherapy of obsessive-compulsive disorder. Pharmacopsychiatry 26 (Suppl. 1), 24–29.

Meck, W.H., 1983. Selective adjustment of the speed of internal clock and memory processes. J. Exp. Psychol.: Anim. Behav. Process. 9 (2), 171–201.

Meck, W.H., 1986. Affinity for the dopamine D2 receptor predicts neuroleptic potency in decreasing the speed of an internal clock. Pharmacol. Biochem. Behav. 25 (6), 1185–1189.

Meck, W.H., 1996. Neuropharmacology of timing and time perception. Brain Res. Cognitive Brain Res. 3 (3–4), 227–242.

Meck, W.H., Church, R.M., 1983. A mode control model of counting and timing processes. J. Exp. Psychol.: Anim. Behav. Process. 9 (3), 320–334.

Molloy, A.G., Waddington, J.L., 1984. Dopaminergic behaviour stereospecific promoted by the D1 agonist R-SK and F 38393 and selectively blocked by the D1 antagonist SCH 23390. Psychopharmacology (Berl) 82 (4), 409–410.

Murray, A.M., Waddington, J.L., 1989. The induction of grooming and vacuous chewing by a series of selective D-1 dopamine receptor agonists: two directions of D-1:D-2 interaction. Eur. J. Pharmacol. 160 (3), 377–384.

Nenadic, I., Gaser, C., Volz, H.P., Rammsayer, T., Hager, F., Sauer, H., 2003. Processing of temporal information and the basal ganglia: new evidence from fMRI. Exp. Brain Res. 148 (2), 238–246.

Odum, A.L., Lieving, L.M., Schaal, D.W., 2002. Effects of D-amphetamine in a temporal discrimination procedure: selective changes in timing or rate dependency? J. Exp. Anal. Behav. 78 (2), 195–214.

Ralph, M.R., Foster, R.G., Davis, F.C., Menaker, M., 1990. Transplanted suprachiasmatic nucleus determines circadian period. Science 247 (4945), 975–978.

Rao, S.M., Mayer, A.R., Harrington, D.L., 2001. The evolution of brain activation during temporal processing. Nat. Neurosci. 4 (3), 317–323.

Richter, C.P., 1967. Sleep and activity: their relation to the 24-h clock. Res. Publ. Assoc. Res. Nerv. Ment. Dis. 45, 8–29.

Robinson, T.E., Berridge, K.C., 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain. Res. Rev. 18 (3), 247–291.

Rylander, G., 1972. Psychoses and the punding and choreiform syndromes in addiction to central stimulant drugs. Psychiatr. Neurol. Neurochir. 75 (3), 203–212.

Saka, E., Goodrich, C., Harlan, P., Madras, B.K., Graybiel, A.M., 2004. Repetitive behaviors in monkeys are linked to specific striatal activation patterns. J. Neurosci. 24 (34), 7557–7565.

Schultz, W., Dickinson, A., 2000. Neuronal coding of prediction errors. Annu. Rev. Neurosci. 23, 473–500.

Wiegant, V.M., Cools, A.R., Gispen, W.H., 1977. ACTH-induced excessive grooming involves brain dopamine. Eur. J. Pharmacol. 41 (3), 343–345.

Wyvell, C.L., Berridge, K.C., 2000. Intra-accumbens amphetamine increases the conditioned incentive salience of sucrose reward: enhancement of reward “wanting” without enhanced “liking” or response reinforcement. J. Neurosci. 20 (21), 8122–8130.