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Research report

Effects of delayed reinforcers on the behavior of an animal model of attention-deficit/hyperactivity disorder (ADHD)

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Abstract

Attention-deficit/hyperactivity disorder (ADHD), affecting 3–5% of grade-school children, is a behavioral disorder characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity. It has been suggested that the symptoms are caused by altered reinforcement and extinction processes, behaviorally described as an abnormally short and steep delay-of-reinforcement gradient in ADHD.

The present study tested predictions from the suggested shortened and steepened delay gradient in ADHD in an animal model, the spontaneously hypertensive rats (SHRs). It was predicted that SHR responding during baseline would mainly consist of responses with short interresponse times, and that responding would be more rapidly reduced in the SHR than in the controls by the introduction of a time interval between the response and reinforcer delivery. Effects of a resetting delay of reinforcement procedure with water as the reinforcer were tested on two baseline reinforcement schedules: variable interval 30 s (VI 30 s) and conjoint variable interval 60 s differential reinforcement of high rate 1 s (VI 60 s DRH 1 s).

The results showed a higher rate of responses in the SHR than in the controls during baseline, mainly consisting of responses with short interresponse times. The statistical analyses showed that response rates decreased more rapidly as a function of reinforcer delay in the SHR than in the controls. The analyses of the estimates of the reinforcer decay parameter showed no strain differences during the VI 30 s schedule but showed a significant strain difference at the end, but not at the start, of the sessions during the VI 60 s DRH 1 s schedule.

In general, the results support predictions from the suggested steepened delay gradient in SHR. However, the predictions were only partly confirmed by the analyses of the decay parameter.

Keywords: Catecholamine; Reward; Hyperkinesis; Hyperkinetic disorder; IRT

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) [2] is the most common behavioral disorder of childhood affecting between 3 and 5% of grade-school children [1,61,63,64]. The core symptoms include a persistent pattern of inattention and/or a developmentally inappropriate level of hyperactivity. Age of onset is usually before the child is 7-year old [3,6]. ADHD is a highly persistent disorder and 50–70% of children diagnosed with ADHD will experience difficulties related to social adjustment and functioning and/or have psychiatric problems as adolescents and young adults [9,67].

ADHD is currently defined as a developmental disorder where all clinical criteria are behavioral. The cause of ADHD has not yet been ascertained and there is no biological marker distinguishing ADHD from normality. However, a strong genetic basis for ADHD has been recognized [14,29,62], and dopamine dysfunction seems to be an important factor in its etiology [19,60,66].

Reinforcers affect the behavior of children with ADHD and normal children differently [18,28,37,42,57], and children with ADHD are less sensitive to changes in reinforcement contingencies compared to normal controls [65].

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Altered reinforcement processes have been suggested as a factor in producing ADHD symptoms [8,17,18,23,42–44,55,68]. ADHD children show aversion to delayed reinforcers and generally prefer immediate reinforcers, even when these are less attractive than reinforcers that may be obtained after a delay [56,57].

Reinforcement and extinction have been demonstrated to be associated with dopamine neuron activity in primates [22,52]. The neurobiological basis for the delay-of-reinforcement gradient may be the time window available for coincidence detection of new response–reinforcement or stimulus–response–reinforcement relations [31]. Dopamine release may, at a neuronal level, increase the time window for coincidence detection. Consequently, reduced dopamine function associated with ADHD may produce narrower than normal time windows for coincidence detection resulting in a shorter than normal delay gradient [23,45].

We have suggested that there might be three underlying factors causing ADHD: a shorter than normal delay-of-reinforcement gradient, deficient extinction of previously reinforced behavior, and poor motor control [23,45]. An abnormally short delay gradient in ADHD implies that only responses in close proximity to reinforcer delivery can be strengthened by the reinforcer [23,39,42,43,49]. A shorter delay gradient may be the source of ADHD children's aversion to delayed reinforcers and their preference for immediate reinforcers, even when more attractive reinforcers may be obtained after a delay, cf. [56,57].

A reinforcer acts not only on the response that produced it but to a lesser degree also on responses emitted earlier [10]. Also relations between responses (e.g. interresponse times, IRTs) are strengthened and maintained by reinforcers [10,13,42]. In contrast to the normal delay gradient, only short IRTs may be reinforced and maintained by a short delay gradient.

The present studies investigated behavioral effects of delayed reinforcers in an animal model of ADHD using a resetting delay-of-reinforcement procedure. The spontaneously hypertensive rat (SHR) is possibly the best-validated animal model of ADHD [40,41]. Bred from normotensive progenitor Wistar Kyoto rats (WKY), SHR have demonstrated attention problems [27,47,48], impulsiveness and hyperactivity (see [40,41]). Also, as in children with ADHD [42], hyperactivity is not present in novel situations, but develops after some time in the new setting [27,48].

In the first part of the present study, predictions derived from a hypothetical shorter and steeper delay gradient in the SHR were experimentally tested. A short and steep delay-of-reinforcement gradient will mainly reinforce responses with short IRTs (burst responding). Consequently, it was predicted that the SHR would develop a high rate of responses with short IRTs when the reinforcers were delivered without any delay. Further, in the resetting delay procedure, the consequence of the lever press (delivery of a drop of water) was delayed for a specified time interval (i.e. the effect of the reinforcer is "blocked"). Thus, a greater proportion of a steep and short delay gradient would be "blocked" as compared to a long and less steep normal delay gradient. Therefore, we also predicted that responding would be more affected by delayed reinforcement in SHR than in control WKY rats.

2. General methods

2.1. Subjects

The subjects in each experiment were eight male NIH-strain spontaneously hypertensive rats (SHR) and 8 male NIH-strain Wistar Kyoto (WKY) control rats bred by a commercial supplier (Møllegaard Breeding Center, Denmark). The subjects were experimentally naive and weighed 180–250 g at the start of each experiment. In experiment 1, the rats were housed in groups of four of the same strain in opaque plastic cages 35 cm × 26 cm × 16 cm (height). During experiment 2, the rats were housed individually in the same type of cages. In both experiments, the animals had free access to food (Beekay Feeds, Rat and Mouse Autoclavable Diet, B&K Universal Ltd.).

A 22 h drinking water-deprivation schedule was used throughout both experiments except during weekends when the animals had free access to water. Access to water in the home cage was limited to 30 min immediately following each session. The animal quarters were temperature and humidity controlled (20 ± 2 °C and 55 ± 10%, respectively). Light was on between 0800 and 2000 h.

The experiment was approved by the Norwegian Animal Research Authority (NARA), and was conducted in accordance with the laws and regulations controlling experiments/procedures in live animals in Norway.

2.2. Apparatus

Eight identical Campden Instruments rodent test cages, 26 cm × 25 cm × 30 cm (height), were located in Campden Instruments small environment cubicles. One 2.8 W house light illuminated each test chamber. The chambers were equipped with two retractable levers requiring 3 g (0.03 N) to close. Only the left lever was used; the right lever remained retracted throughout the experiments. One liquid dipper delivered 0.01 ml of tap water when activated. It was housed in a small cubicle with a 2.8 W cue light and located halfway between the two levers. A 7 cm × 5 cm transparent, top-hinged plastic flap separated this cubicle from the animal's working space. Light pushing by the nose or the paw was sufficient to open the flap and activated a microswitch. A computer and an on-line system (Spider, Paul Fray Ltd., UK) recorded lever presses and tray visits, and scheduled reinforcers and lights. Behavior was also recorded by cumulative recorders.

2.3. General procedure

2.3.1. Response shaping

During the combined 15 min habituation and magazine training sessions, the animals received water according to a variable time 3 s schedule (VT 3 s). This schedule presents a reinforcer on average every 3 s independent of the animal's behavior. In these sessions, the flap in front of the water dipper remained open.

The habituation and magazine training sessions were followed by two sessions where opening of the flap into the water cubicle

was shaped. Flap openings activated the dipper and lit the cubicle light. The lever was retracted during habituation and magazine training.

Two sessions followed in which pressing the left lever was shaped according to the method of successive approximation [11]. Each lever press operated the liquid dipper and lit the cubicle light. The water was available for 3 s after opening of the flap. The water dipper was lowered and the cubicle light turned off if the water was not collected within 5 s. Three sessions followed with reinforcement of every lever press (FR1).

The sessions were run between 1600 and 1800 h, 5 days per week. The animals were run in the same order and in the same chamber every day. Times of testing were balanced so that subjects from the two strains were equally distributed.

2.3.2. Statistics

The behavior was considered stable when a visual examination of the total number of responses revealed no systematic trends. The last five sessions from each condition were used in the statistical analyses. Mondays were excluded because of greater than normal variability in behavior, presumably due to variation in deprivation duration.

Data were evaluated by multivariate analyses in the Statistica program [59] using Wilks lambda (MANOVAs) when the degrees of freedom compared to number of levels of the repeated factor permitted this approach, and by univariate analyses of variance (ANOVAs) adjusting the degrees of freedom with the Huynh–Feldt epsilon [34].

Curve-fitting was performed on data averaged for each condition using an iterative procedure in the SPSS for Windows, version 11.0 [58], with the sums of squared residuals loss function and the Levenberg–Marqardt algorithm. Independent samples *t*-tests were used for evaluating parameter estimates in the VI input–output function [58].

A 5%-level of statistical significance was used in all analyses.

3. Experiment 1

3.1. Method

3.1.1. Random interval 30 s schedule of reinforcement (RI 30 s)

Seven sessions of habituation, magazine training, and shaping of flap openings and lever presses were conducted before a random interval 30 s (RI 30 s) schedule of reinforcement was installed (see Table 1). This schedule was run for 40 sessions in order to stabilize behavior before testing the effects of delaying the reinforcer. In RI schedules, the first correct response after a reinforcement set-up will produce the reinforcer. The set-up will be made according to a fixed probability every *t* s. The average interval in the RI schedule equals *t* divided by the probability [11]. The time between reinforcers in RI schedules varies unpredictably, but with a specified mean time. If a new reinforcer is set-up before the previous has been delivered, the new one will be programmed immediately after the delivery of the previous. This procedure ensures a relatively equal number of reinforcers to all animals.

Table 1
Summary of the experimental procedure

Schedule	Session number (number of sessions)	Note
Experiment 1		
Habituation/magazine training	(3)	22 h water deprivation
Response shaping		
Door openings	(2)	No lever
Lever presses	(2)	Left lever installed
FR1	8–11 (4)	Left lever installed
RI 30 s	12–55 (40)	Left lever installed
RI 30 s RD 3.0 s	56–65 (10)	Left lever installed
RI 30 s RD 0.0 s	66–76 (11)	Left lever installed
RI 30 s RD 1.0 s	77–85 (9)	Left lever installed
RI 30 s RD 0.33 s	86–93 (8)	Left lever installed
Experiment 2		
Habituation/magazine training	(3)	22 h water deprivation
Response shaping		
Door openings	(2)	No lever
Lever presses	(2)	Left lever installed
FR1	(3)	Left lever installed
VI 60 s DRH 1 s	4–38 (35)	Left lever installed
VI 60 s DRH 1 s RD 0.5 s	39–52 (14)	Left lever installed
VI 60 s DRH 1 s RD 1.0 s	53–67 (15)	Left lever installed
VI 60 s DRH 1 s RD 2.0 s	68–81 (14)	Left lever installed
VI 60 s DRH 1 s RD 4.0 s	82–102 (21)	Left lever installed
VI 60 s DRH 1 s RD 8.0 s	103–116 (14)	Left lever installed
VI 60 s DRH 1 s RD 12.0 s	117–130 (14)	Left lever installed
VI 60 s DRH 1 s RD 16.0 s	131–145 (15)	Left lever installed
VT 60 s	146–166 (21)	Left lever installed
VI 60 s DRH 1 s RD 4.0 s	167–184 (18)	Left lever installed

FR1: fixed ratio 1; RI: random interval; RD: reinforcer delay; VI: variable interval; DRH: differential reinforcement of high rate.

3.1.2. Tandem random interval 30 s non-signaled resetting delay of reinforcement schedule

The final schedule was a tandem random interval 30 s non-signaled resetting delay *x* s (RI 30 s RD *x* s). A schedule is termed tandem when completion of one schedule component produces another component, and completion of this component produces the reinforcer [11]. In the RI 30 s RD *x* s, the first correct response after reinforcer set-up completes the first component, RI 30 s. The second component, non-signaled RD *x* s, requires that the lever switch is not closed during the next *x* s. Lever pressing during the delay resets the delay interval, but does not return the schedule to the RI component.

The RI 30 s schedule of reinforcement will hereafter be referred to as the 0 s delay. Experiment 1 examined four delays: 0, 0.33, 1.0 and 3.0 s. The delays were run in the following order: 0, 3, 0, 1 and 0.33 s. The 0 s delay after the 3 s delay was used to stabilize behavior before running the 1.0 and 0.33 s delays (see Table 1 for a summary of the experimental procedure).

The sessions lasted 15 min plus the delay intervals and the time required to consume the reinforcers. Accordingly, duration of sessions varied. The longest sessions were those with the 3 s delay.

The sessions were divided into three 5 min segments in order to measure within-session changes in behavior. Lever presses, number of reinforcers produced and collected, and openings of the flap into the water cubicle (tray visits) were recorded by the computer. The times between two consecutive lever presses, interresponse times (IRTs), were also recorded. The IRTs were grouped into 16 consecutive 0.2 s bins: $0\,s < IRT < 0.2\,s$, $0.2\,s < IRT < 0.4\,s$, ..., $IRT > 3.0\,s$. These bins served as the basis for the IRT analyses.

3.2. Results

An increase in number of responses with short IRTs during the initial training was observed in the SHR, but not in the controls (Fig. 1, upper panel). Total number of responses, however, was stable in both strains.

In general, the SHR had a higher rate of responses during the 0 s delay, mainly consisting of responses with short IRTs (Fig. 2, upper panel; Fig. 3, upper panel). This strain difference was gradually reduced by increasing reinforcer delay, and was non-existent at the 3 s delay. Compared to the controls, the SHR also opened the flap into the water cubicle more at all delays, with the exception of the 3 s delay where the strain difference was reversed (Fig. 4, upper panel).

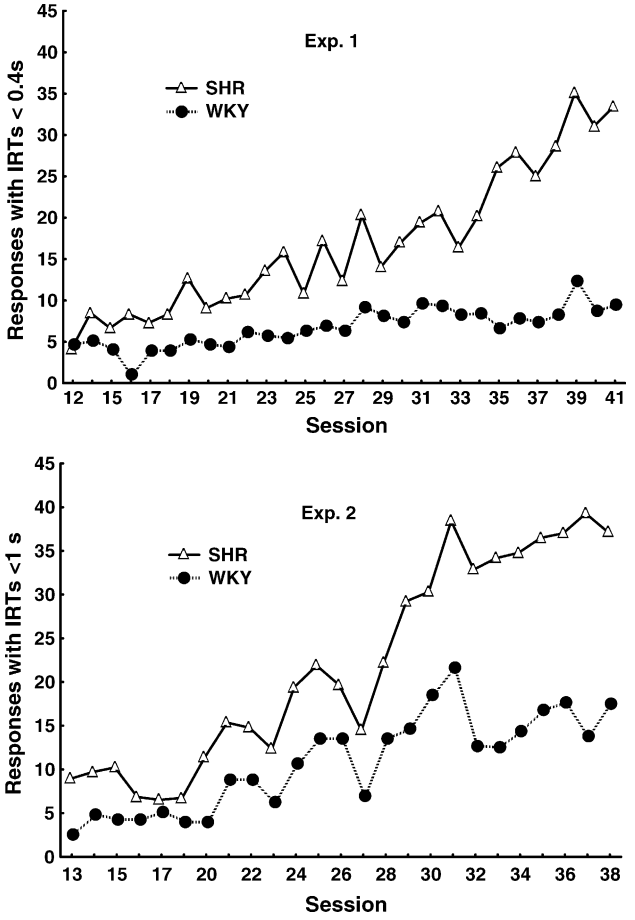

Fig. 1. The development of responses with short interresponse times (IRTs < 0.4 s) during the RI 30 s schedule with no delay (upper panel), and development of the operant (IRTs < 1 s) during the conjoint VI 60 s DRH 1 schedule with no reinforcer delay (lower panel).

3.2.1. Lever presses

The SHR emitted more lever presses per minute than the controls, especially during the 0 s delay (Fig. 2, upper). With increasing reinforcer delays, both strains showed a decline in lever pressing, the decline being steeper in the SHR than in the controls. At the 3.0 s delay, the strains had almost equal rates of lever pressing. The rate of lever presses in the SHR increased from the first segments to the second segments and then stabilized. Rate of responding in the controls, however, decreased across the three segments. The analyses showed a significant main effect of strain, $F(1, 14) = 12.85$; $p < 0.01$, a significant strain by delay interaction effect, $F(3, 12) = 4.07$; $p < 0.05$, and a strain by segment interaction effect, $F(2, 13) = 11.47$; $p < 0.01$. Further, the ANOVA showed a significant strain by delay by segment interaction effect, $F(2.07, 28.91) = 10.55$; $p < 0.001$, that was not confirmed by the MANOVA, $F(6, 9) = 3.00$; $p = 0.068$.

3.2.2. Estimating parameters in the decay function

In a separate analysis, the hyperbolic decay function for each individual rat was fitted to the number of lever presses per minute as a function of reinforcer delay duration:

$$V = \frac{A}{1 + KD} \quad (1)$$

The parameter V represents the reinforcer value when delivered after a delay, D, A the reinforcer value when the reinforcer is delivered immediately, and K is the parameter describing the rate of decay [32]. A curve-fitting program [59] was used to find the least square fits of A and K in the hyperbolic decay function (1). The program uses an iterative procedure, varies the parameters, and progressively reduces the increments of the parameter values tested until each estimate is accurate to four decimal places.

The previous analyses of lever pressing showed statistically significant strain by segment interaction effects. Therefore, estimations of A and K were performed separately for total rate of responding as well as for responding during the first and the last segment of the session.

A good fit of the hyperbolic function for the behavioral output across the delay intervals was obtained for all animals. The explained variance ranged from 0.86 to 0.99 (mean = 0.96) for curve fits using the total response rates for the entire session. The explained variance for curve fits to response rates during the first segment ranged from 0.90 to 0.99 (mean = 0.96), and from 0.49 to 0.99 (mean = 0.91) for response rates during the last segment.

The estimates of A for total response rate (all three segments) were significantly higher in the SHR compared to the controls, $t(14) = 2.96$; $p < 0.05$, while there were no strain difference in estimates of K. The comparisons of A and K in the two strains during the first segment showed no statistically

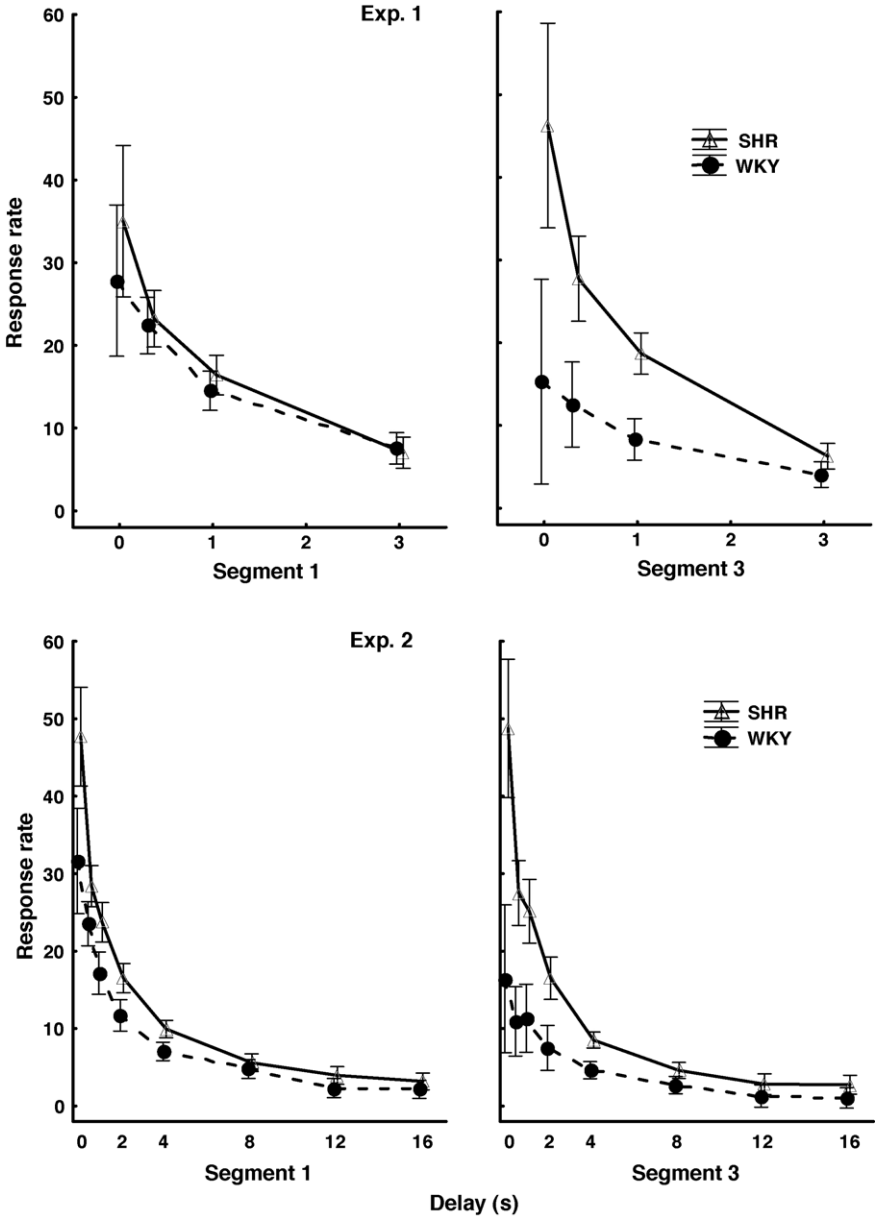

Fig. 2. Lever presses per minute (95% CI) as a function of reinforcer delay during the RI 30 s schedule (upper panel) and during the conjoint VI 60 s DRH 1 s schedule (lower panel).

significant strain difference. Analyses of the responding during the last segment showed that the estimates of *A* in the SHR were higher than in the controls, $t(14) = 3.79$; $p < 0.01$. The analyses showed no statistically significant strain differences in parameter *K* (see Table 2 for estimates of parameter means).

3.2.3. IRT distributions

The absolute number of responses was used in the analyses of the IRT distribution. Reinforcer delay affected the two strains differently. At no delay (RI 30 s), the SHR emitted approximately five times as many responses with short IRTs (0 s < IRT < 0.2 s) as the controls. This difference decreased with increasing delay of reinforcement, and was non-existent

Table 2
Mean estimates of parameters *A* and *K* in the hyperbolic decay equation across the entire session and during the first and the last segments in experiments 1 and 2

	Entire session		Segment 1		Segment 3	
	A	*K*	*A*	*K*	*A*	*K*
Experiment 1						
SHR	43.47*	1.83	35.98	1.55	47.67*	2.00
WKY	22.66*	0.90	28.64	1.03	15.76*	1.06
Experiment 2						
SHR	49.12*	1.10	47.55*	1.06	48.76*	1.11*
WKY	24.07*	0.76	32.25*	0.87	16.36*	0.64*

* $p < 0.05$.

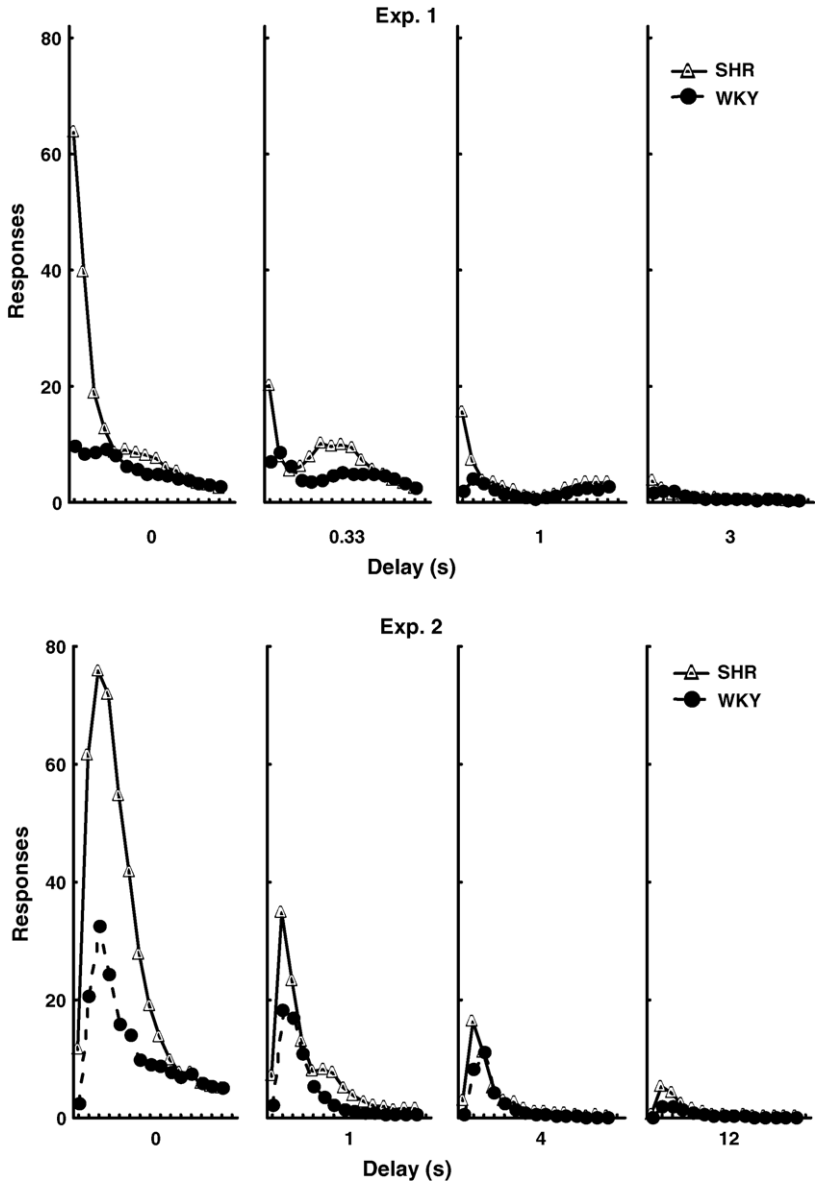

Fig. 3. Interresponse time distributions divided into 0.2 s-bins as a function of delay during the RI 30 s schedule (upper panel) and distributions divided into 0.1 s-bins across selected delays during the conjoint VI 60 s DRH 1 s schedule (lower panel).

at the 3.0 s delay (Fig. 3, upper panel). Also, at the 0.33 s delay there was an increase in responses with intermediate IRTs in the SHR.

The ANOVAs showed a statistically significant strain by IRT effect, $F(1.75, 24.54) = 4.57$; $p < 0.05$, a strain by delay by IRT interaction effect, $F(1.73, 24.27) = 4.61$; $p < 0.05$ (Fig. 3, upper panel), a significant strain by segment by IRT interaction effect, $F(3.64, 51.02) = 4.33$; $p < 0.01$, and a significant strain by delay by segment by IRT interaction effect, $F(4.42, 61.85) = 4.01$; $p < 0.01$.

3.2.4. Reinforcers

The two strains produced, and collected, approximately 10 reinforcers in every segment of the session, a total of 30 reinforcers for the entire session.

3.2.5. Tray visits

Generally, the SHR opened the tray lid more than the controls except during the 3.0 s delay (Fig. 4, upper panel). In the SHR, the rate of unnecessary tray visits increased from the 0 s delay to the 0.33 s and 1.0 s delays, with an abrupt decrease at 3.0 s delay, while the rate of unnecessary tray visits was constant across the segments. In the controls, the rate of unnecessary tray visits increased across the delays and decreased across segments.

The analyses showed no significant main effect of strain, $F(1, 14) = 3.73$; $p = 0.07$. However, there were significant strain by delay, $F(3, 12) = 3.96$; $p < 0.05$ (Fig. 5, upper panel); strain by segment, $F(2, 13) = 11.44$; $p < 0.01$; and a strain by delay by segment interaction effects, $F(6, 9) = 3.41$; $p < 0.05$.

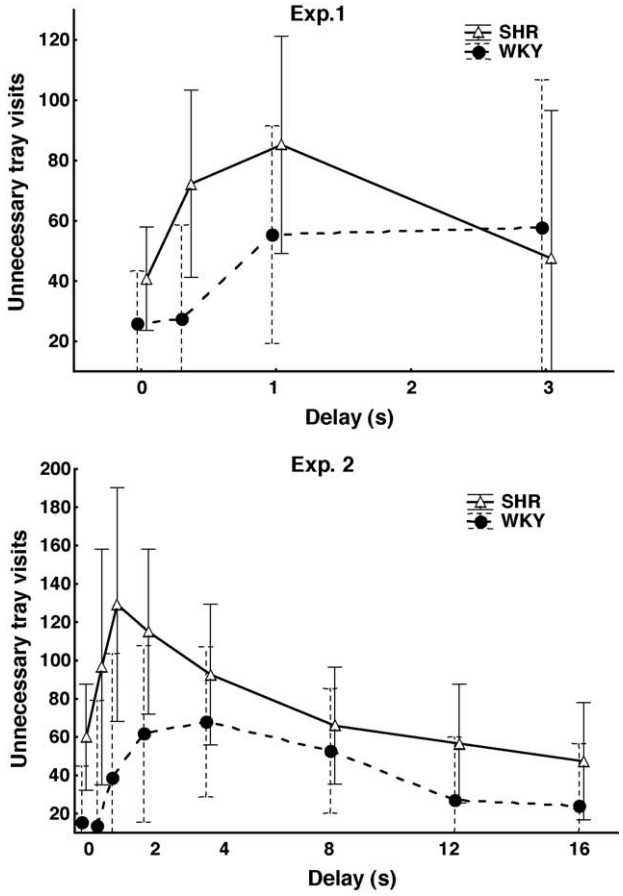

Fig. 4. Unnecessary tray visits (95% CI) as a function of delay duration during the RI 30 s schedule (upper panel) and during the conjoint VI 60 s DRH 1 s schedule of reinforcement (lower panel).

3.3. Discussion

This study experimentally tested predictions from the hypothesis of a steeper and shorter delay-of-reinforcement gradient in the SHR compared to the controls. A shorter delay gradient implies that the reinforcer will mainly have an effect on responses in close temporal proximity to the delivery of the reinforcer, and that mainly responses with short IRTs will be reinforced. The behavior of the SHR was, therefore, predicted to be more sensitive to delayed reinforcement than the controls' behavior. By introducing increasingly longer resetting delay intervals, a more pronounced reduction of responding in the SHR compared to the controls was predicted.

The results showed that the SHR were slightly less active than the controls at the start of the study (Fig. 1, upper panel), supporting earlier findings that SHR are not hyperactive in novel settings [27,48]. During the course of the experiment, the SHR developed a high rate of responses, mainly consisting of responses with short IRTs. At baseline, before delayed reinforcement was introduced, about five times as many responses with short IRTs were recorded for the SHR compared to the controls. Introducing a resetting delay interval caused a more rapid reduction in responding in the SHR than in controls. At 3.0 s delay interval there was no strain difference in burst responding (Fig. 3, upper panel). These results are consistent with a steeper and shorter delay gradient in the SHR compared to controls.

In order to test the rate of decay of responding as a function of reinforcer delay in the two strains, an iterative procedure was used fitting the hyperbolic decay function to the behavioral output during the delays for estimating the parameters A (the reinforcer efficacy at no delay) and K (the rate of decay in reinforcer efficacy). Overall, the results showed that that the estimates of A were statistically significantly higher in the SHR compared to the controls across all segments. Estimates of K were generally higher in the SHR, but were not statistically significantly different from the controls (Table 2 and Fig. 2, upper).

The number of unnecessary tray visits also changed systematically in both strains as a function of reinforcer delay duration. Compared to the controls, the SHR had more visits except during the 3 s delay. Imposing a delay between the reinforcer-producing response and delivery of the reinforcer provides an opportunity for tray visits between the lever press and the delivery of the reinforcer. The delivery of reinforcers after short delays may reinforce tray visits occurring in the delay interval. The increased rate of tray visits during short delay intervals may, therefore, be interpreted as fortuitous reinforcement and maintenance of "superstitious" behavior [54]. It is possible that the reduction in lid openings in the SHR during the 3 s delay resulted from an increased sensitivity to the temporal response–reinforcer relations, consistent with a shorter delay of reinforcement gradient.

The effects of delayed reinforcement have been extensively studied in animals by manipulating several aspects of the reinforcement contingencies. The plethora of different procedures demonstrates the complexity of delayed reinforcement. The delay period may be signaled (e.g. [5,16,20,30,33,35,36,38,50,51]) or unsignaled (e.g. [4,12,15,53,71]). The opportunity to respond may be withdrawn during the delay interval (e.g. [36]) or a "blackout" procedure during the delay may be used (e.g. [35]). Responding during the delay interval may be non-functional (e.g. [4,30,33,38]), may be functional by resetting the delay interval (e.g. [5,15,16,69]) or another component of the reinforcement schedule (e.g. [21]), or program the delivery of a new reinforcer, "stacked delay" (e.g. [69]).

The various delay-of-reinforcement procedures result in various rates of behavior as a function of the time interval imposed between response and reinforcer and as a function of the specific delay procedure employed. Two related problems are how to ensure a precise delay interval between the last response and reinforcer presentation without changing the reinforcement contingencies, and how to treat responses emitted in the delay interval. If these responses are non-functional (non-resetting), the procedure will not ensure a specified delay interval between the last response and reinforcer presentation. In resetting procedures, however, resetting the delay interval as a consequence of responding may be described as

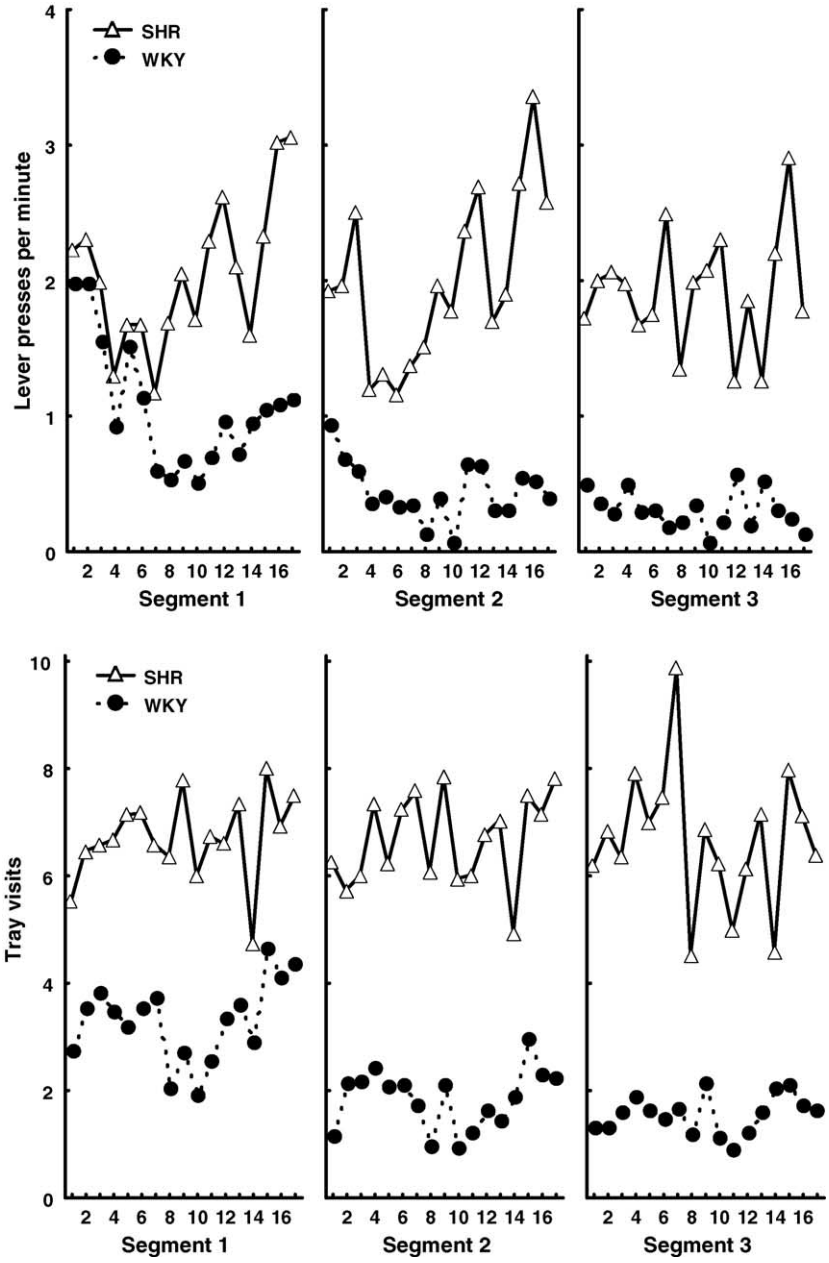

Fig. 5. Lever presses (upper) and tray visits (lower) across the three segments during seventeen sessions running the variable time 60 s schedule.

a response suppressing contingency (i.e. postponing the reinforcer), creating difficulties for subsequent interpretation of the results. Measuring the reinforcer effect by response rate, the reduced response rate during resetting delay procedures may be an effect of both the delay interval and the changed contingencies, and it is difficult to determine the effect of the delay interval alone.

Another important factor in delay procedures is whether the delay interval is signaled or not. Signaled delay procedures interpose a stimulus between the response and the reinforcer. Hence, responding is not only a function of delay per se, as the signal may function as an immediate conditioned reinforcer, which "bridges" the time interval between the response and reinforcer presentation.

Here, the SHR developed a high rate of response with short IRTs during the baseline condition before the delay procedure was imposed. More short IRTs during no delay indicate a selective reinforcer effect on these responses due to a steepened delay of reinforcement gradient. However, short IRTs have been described as a variant of single responses with two lever presses instead of one [7]. Schedules reinforcing and maintaining long IRTs (e.g. differential reinforcement of low rate, DRL) tend to produce a bimodal IRT distribution. One peak consisting of responses with short IRTs not

being affected by the contingencies and a second peak being a function of the schedule requirement (see [10]). Similar results are observed in the SHR when long-lasting "passive" responses are reinforced [70] or long DRL schedules are used [44]. The responses with short IRTs observed in the SHR in the present study, however, both developed during the experiment and were modifiable by the resetting delay procedure, which suggest that they were controlled by the reinforcement contingencies. Thus, the short IRTs reinforced and maintained by the RI 30 s RD *x* s schedule seem different from the short IRTs maintained by DRL schedules. However, responses with short IRTs during no delay can be emitted at a free rate, while the delay interval length limits responses with short IRTs during the resetting delay interval procedure. Responses with IRTs shorter than the delay interval will reset the interval except in the rare instances where reinforcer set-up has been made in the time interval between two responses. Therefore, a change in response rate, and especially in rate of IRTs shorter than the delay interval, does not necessarily reflect a change in reinforcer effect, but may reflect a response suppressing contingency.

Due to the uncertainties regarding the role of responses with short IRTs, a second experiment was designed to study the effect of delayed reinforcement when short IRTs were a requirement of the reinforcement schedule. To reduce the strain difference in rate of responses with short IRTs, possibly interacting with the response-suppressing effects of delayed reinforcement, a differential reinforcement of high rate (DRH) schedule of reinforcement was used to reinforce responses with short IRTs in both strains before introducing reinforcer delay.

Included in the experimental protocol was a condition where reinforcers were presented independently of responding using a variable time (VT) schedule of reinforcement. This condition was included in order to compare the rate of responding during delayed reinforcement with rate of responding retained when responding had no consequences. It was hypothesized that this comparison would enable an estimate of response output when reinforcers had stopped controlling behavior during delayed reinforcement.

As during the first experiment, we predicted that a higher rate of responses with short IRTs in the SHR would develop during no reinforcer delay and that responding in the SHR would be more sensitive to reinforcer delay. Further, we predicted that the reinforcers stopped controlling SHR behavior at shorter reinforcer delay intervals than in the controls.

4. Experiment 2

4.1. Method and procedure

Habituation, magazine training, and shaping of flap openings and lever presses were performed as in experiment 1 (see Table 1). Thereafter a conjoint variable interval *x* s differential reinforcement of high rate 1 s (conjoint VI *x* s DRH 1 s) was installed. The interval in the VI component was gradually increased from 1 to 60 s. A total of 38 sessions were run before the delay-of-reinforcement conditions were introduced.

In VI schedules, the first correct response after a reinforcement set-up will produce the reinforcer [11]. The reinforcers are set-up according to a predetermined sequence of intervals with a specified mean time. In VI 60 s, there will be one reinforcer setup on the average every 60 s. As the reinforcers vary unpredictably, VI schedules produce and maintain a relatively stable rate of responding.

In DRH schedules, a response is reinforced if at least *n* responses were emitted during the last *t* seconds. The DRH 1 s schedule used in the present experiment requires two lever presses within 1 s to produce a reinforcer. Responses more than 1 s apart were never reinforced.

A schedule is called conjoint when two or more component schedules are operating for a single response [11]. The conjoint VI 60 DRH 1 schedule reinforces the first response with a short IRT (IRT > 1 s) after the reinforcer has been set-up by the VI component (on the average every 60 s).

The non-signaled resetting reinforcer delay *x* s (RD *x* s) schedule requires that the lever switch is not closed during the next *x* s. Lever pressing during the delay resets the delay interval, but does not return the schedule to the first (conjoint VI 60 DRH 1) component.

The final schedule of reinforcement was a tandem (conjoint VI 60 DRH 1) non-signaled resetting delay *x* s (RD *x* s). The rat had to complete both schedule components (VI DRH and RD) in order to for a reinforcer to be delivered. None of the components were signaled (tandem). The contingencies can be described in the following way: after the reinforcer is set-up by the VI component, one response with an IRT < 1 s and then not responding for *x* s produces the reinforcer. If a new reinforcer were set-up before the previous has been delivered, the new one would be programmed immediately after the delivery of the previous. This procedure will ensure that all animals obtain an approximately equal number of reinforcers.

This experiment examined eight reinforcer delay intervals: 0.0, 0.5, 1.0, 2.0, 4.0, 8.0, 12.0, and 16.0 s. The session lasted 30 min plus the delay intervals and the time required to consume the reinforcers. Accordingly, duration of sessions varied. The longest sessions were those with the 16 s delays. The rats received approximately 30 reinforcers.

Towards the end of the experiment, after the 16 s delay, a control condition was run in order to determine the rate of responding maintained in each strain when the response–reinforcer contingency was broken ("operant level"). A VT 60 s schedule served this purpose, delivering reinforcers non-contingent upon lever presses. The time between reinforcers varied with a mean of 60 s.

After the VT condition, the 4 s delay condition was replicated in order to check the reliability of the experimental procedure. The analyses found no statistically significant differences between the two 4 s delay conditions confirming the reliability of the procedure.

The session was divided into three 10 min segments in order to measure within-session stability. During each session, lever presses, tray visits, number of reinforcers produced, and IRTs were recorded. IRTs were grouped into sixteen 0.1 s bins: 0 s < IRT < 0.1 s, 0.1 s < IRT < 0.2 s,. . ., 1.3 s < IRT < 1.4 s, and IRT > 1.5 s.

One WKY control rat was excluded from the data analysis because it was an extreme outlier, showing markedly deviant behavior as compared to the other controls.

4.2. Statistics

The results were analyzed as described in Section 2.3. In addition, mean response rates for the five last VT sessions were compared to response rates during each of the delays using Newman–Keuls tests [59].

4.3. Results

Rate of responses with short IRTs increased across the initial sessions in both strains, but more in the SHR than in the controls (Fig. 1, lower panel). Higher response rates were found in the SHR than in the controls during short delays, while this difference decreased during long reinforcer delays. Also, the SHR opened the flap into the water cubicle more often than the controls, especially during short delays (Fig. 4 lower).

4.3.1. Lever presses

The SHR demonstrated an elevated overall rate of lever presses per minute as compared to the controls. The strain difference was most pronounced during delays of 2 s and shorter (Fig. 2, lower panel). There was a significant main effect of strain $F(1, 13) = 50.52$; $p < 0.001$ and a significant strain by delay interaction effect, $F(7, 7) = 6.63$; $p < 0.05$ (Fig. 2, lower panel).

The rate of lever presses decreased across segments in the controls, while the SHR showed a steady response rate across segments. There were significant strain by segment, $F(2, 12) = 38.26$; $p < 0.001$, and strain by delay by segment interaction effects, $F(6.61, 85.95) = 13.58$; $p < 0.001$.

4.3.2. Estimating parameters in the decay function

The hyperbolic decay function was fitted for each rat to the number of lever presses per minute as a function of delay interval length using the same curve-fitting program and procedure as in the first experiment.

Due to the statistically significant strain by segment interaction effects found in the previous analyses, estimates of A and K were performed separately for total rate of responding, as well as for responding during the first and the last segments of the session.

The hyperbolic function showed a good fit for the behavioral output across the delay intervals for all animals. The explained variance ranged from 0.94 to 0.99 (mean = 0.97) for curve fits using total response rate, while explained variance ranged from 0.95 to 0.99 (mean = 0.97) during the first segment and from 0.78 to 0.99 (mean = 0.93) during the last segment.

The estimates of A for the total response rate (all three segments) showed similar results to those obtained in experiment 1 (see Table 2). The analyses showed statistically significant higher A in the SHR compared to the controls, $t(13) = 5.16$; $p < 0.001$, while there were no strain difference in K, $t(13) = 2.05$; $p = 0.066$.

The analyses of responding during the first segment showed statistically significant higher A in the SHR compared to the controls, $t(13) = 3.80$; $p < 0.01$, while there were no statistically significant strain differences in estimated K, $p = 0.26$. The analyses of the responding during the last segment showed that the estimates of both A and K in the SHR were statistically significantly higher than in the controls, $t(13) = 5.63$; $p < 0.001$, $t(13) = 2.38$; $p < 0.05$, respectively (see Table 2 for mean parameter estimates).

4.3.3. The operant class

Using a DRH 1 s schedule, only responses with IRTs < 1 s were reinforced, and define the operant descriptive class of responses. The number of lever presses with IRTs < 1 s increased across initial sessions in both strains (Fig. 1, lower panel). Both the SHR and the controls developed response bursts, but the levels were higher in the SHR. Delaying the reinforcer affected the operant responding of the SHR to a larger extent than that of the controls (Fig. 3, lower panel). The analyses showed a significant main effect of strain, $F(1, 13) = 15.28$; $p < 0.01$; a trend for a strain by delay effect, $F(7, 7) = 3.77$; $p = 0.05$; a significant strain by segment effect, $F(2, 12) = 15.56$; $p < 0.001$; and a significant strain by delay by segment interaction effect, $F(6.47, 84.17) = 6.17$; $p < 0.001$.

4.3.4. Reinforcers

Despite saving programmed reinforcers for later delivery, the controls produced fewer reinforcers than the SHR at delays longer than 4 s. The SHR collected more reinforcers than the controls, $F(1, 13) = 8.78$; $p < 0.05$, during short and long reinforcer delays.

4.3.5. Tray visits

The SHR opened the flap into the water cubicle without a reinforcer present more often than the controls. Tray visits in the two strains were differently affected by reinforcer delay. The SHR showed the highest number of tray visits during the 1 s delay, while the controls reached their highest level during the 4 s delay. The analyses showed a statistically significant main effect of strain, $F(1, 13) = 19.66$; $p < 0.001$. The ANOVA also showed a statistically significant strain by delay interaction effect, $F(5.05, 65.59) = 4.24$; $p < 0.01$, which was not confirmed by the MANOVA, $F(7, 7) = 1.46$, $p = 0.3$ (Fig. 4, lower panel). The strains were differently affected across segments. There was a significant strain by segment, $F(2, 12) = 6.52$; $p < 0.05$, and strain by delay by segment interaction effect, $F(7.38, 95.94) = 2.46$, $p < 0.05$.

4.3.6. Comparing behavior during VT (operant level) and delay conditions

The VT schedule was run for 21 sessions, and the last five sessions were used as a baseline for operant level of responding when the reinforcement contingency was terminated. Each strain's behavior during the eight delays (0–16 s) was compared with the operant level during the VT schedule in order to determine when the reinforcers no longer controlled the behavior. Due to the statistically significant strain by segment effects found in the previous experiment, the comparison was performed for responding during each segment separately. In addition, these comparisons were performed separately for responses in the operant class (responses with IRTs < 1 s) and outside the operant class (responses with IRT > 1 s).

No strain differences were found for analyses of responses in the operant class. In both strains, response rates during delays ≥8 s were not statistically significantly different from response rates during VT. Analyses of rates of responses with IRTs > 1 s during the first segment showed no difference between VT and delays ≥12 s, and no strain differences were found. Analyses of the last two segments showed that VT was not statistically significantly different from delays ≥8 s in the SHR, while this was true for delays ≥12 s in the controls.

4.3.7. Behavior during the variable time schedule (VT) condition

The VT schedule was run without any alterations between response-dependent and response-independent reinforcer deliveries. Four out of the total 21 sessions running the VT schedule were excluded from the analyses due to incorrect deprivation length.

4.3.7.1. Lever presses. The analyses showed that more lever pressing was retained in the SHR than in the controls across the 17 sessions, reflected in a significant main effect of strain $F(1, 13) = 4.96$; $p < 0.05$ (Fig. 5, upper). The ANOVA with Huynh–Feldt corrections showed a statistically significant strain by segment interaction effect, $F(2, 26) = 4.52$; $p < 0.05$, which was not confirmed by the MANOVA, $F(2, 12) = 3.34$; $p = 0.07$.

The last five sessions were used as the operant level for comparisons with response rates during reinforcer delays. The three segments analyzed separately showed no significant strain differences during segments 1 and 2, but showed that more responses were retained in the SHR during segment 3 reflected in a main effect of strain, $F(1, 13) = 5.72$; $p < 0.05$.

4.3.7.2. Tray visits. The analyses showed that more visits were maintained during VT in the SHR than the controls across the 17 sessions reflected in a main effect of strain, $F(1, 13) = 20.93$; $p < 0.001$ (Fig. 5, lower). The analyses also showed a statistically significant strain by segment effect, $F(2, 12) = 5.46$; $p < 0.05$, and a significant strain by segment by session effect, $F(14.94, 194.3) = 2.02$; $p < 0.05$.

Separate analyses of tray visits during each of the three segments during the five last sessions showed no strain difference in segment 1, but more tray visits in both segments 2 and 3 by the SHR reflected in significant main effects of strain, $F(1, 13) = 18.43$; $p < 0.001$ and $F(1, 13) = 28.06$; $p < 0.001$, respectively.

4.3.7.3. Reinforcers collected. More reinforcers were collected by the SHR across the 17 session, reflected in a main effect of strain, $F(1, 13) = 9.34$; $p < 0.01$. The ANOVA also showed a strain by segment interaction effect, $F(2, 26) = 5.42$; $p < 0.05$, that was not confirmed by the MANOVA, $F(2, 12) = 3.47$; $p = 0.06$.

The number of reinforcers collected was analyzed separately for the three segments during the five last sessions. The analyses showed no significant strain differences during segment 1, but the SHR collected more reinforcers during segments 2 and 3 as shown by the significant main effects of strain, $F(1, 13) = 6.12$; $p < 0.05$ and $F(1, 13) = 7.59$; $p < 0.05$, respectively.

5. General discussion

The present experiments investigated the effects of delayed reinforcement on the behavior of the SHR, an animal model of ADHD. We hypothesized that imposing a delay interval between the response and reinforcer delivery would weaken the reinforcer effect more in SHR due to the suggested steepened delay gradient compared to normal controls. Both experiments showed essentially the same pattern of results consistent with a delay gradient with different properties in SHR. Responding in the SHR during intermittent reinforcement and no delay consisted of more responses with short IRTs and was more affected by reinforcer delay than in the controls.

The delay gradient can be characterized by three parameters. The initial height, A, the length, B, and the steepness, C (Fig. 6). Hence, the changes in basic learning mechanisms

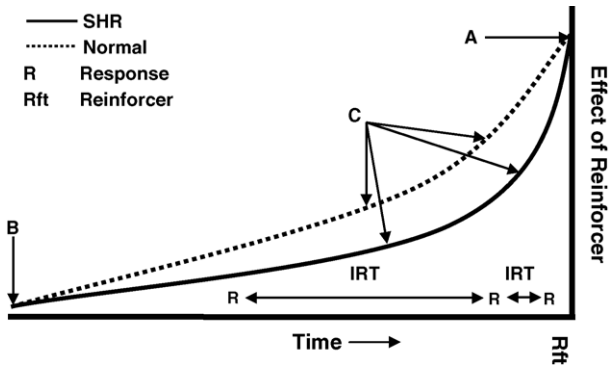

Fig. 6. The delay-of-reinforcement gradient can be characterized by three parameters: the initial height (A), the length (B), and the slope (C). Based on an integration of the present findings, the figure depicts a theoretical steepened delay-of-reinforcement gradient in SHR compared to normal controls having a selective effect on short interresponse times and producing an increased sensitivity to reinforcer delay.

suggested in ADHD and SHR may be described by alterations in these parameters. In the following, the present data are explored in relation to characteristics of delay gradient in SHR compared to controls.

5.1. The height of the delay gradient in SHR

In the present study, response rates mainly consisting of responses with short IRTs were higher in the SHR than in the controls in both experiments when using intermittent reinforcement schedules with no reinforcer delay. This is consistent with the higher estimates of parameter *A* in the hyperbolic equation in SHR. However, using intermittent reinforcement schedules, parameter *A* not only represents the initial height of the delay gradient but also the strengthening of responses previous to the one that produced the reinforcer [10], i.e. the entire delay gradient. Hence, the higher response rates produced by the SHR than the controls during intermittent reinforcement in the present experiments may reflect strain differences in initial height of the delay gradients as well strain differences in the entire delay gradient, e.g. length or height.

A previous study found that SHR were overactive during intermittent reinforcement, consistent with the present findings, but also showed that response rates during frequent reinforcement were the same in SHR and controls [46]. Response rates during frequent reinforcement may reflect the initial height of the delay gradient. This is based on the suggestion that the effect of one reinforcer does not extend beyond the presentation of the previous reinforcer, i.e. the effect is "truncated" by the previous reinforcer. During high reinforcer frequencies, most of the gradient will be truncated, leaving only the initial part functional [13]. Hence, previous findings suggest that the initial height of the delay gradient is equal in SHR and controls (Fig. 6).

When analyzing the relationship between responding, the delay gradient, and reinforcer effect, it is of paramount importance to identify whether the behavioral elements consists of single responses or several responses in a response-burst, and how reinforcement of the temporal relation between responses may affect total response rates. Thus, whether short IRTs are viewed as instances of single responses, two responses in rapid succession constituting one behavioral element, or instances of response-bursts (i.e. a series of short IRTs constituting one behavioral element) have important implications for analyses of reinforcer strength in terms of number of behavioral elements maintained by the reinforcer. The large number of responses with short IRTs in the SHR may actually have consisted of a considerable lower number of behavioral elements. The nature of the behavioral element, therefore, has implications for estimates of total effect of reinforcers in the SHR relative to the controls.

It is not possible to determine the number of lever presses in the two strains' response elements, as no direct behavioral recordings were made. However, in experiment 2 during no reinforcer delay an estimate can be made by dividing the number of lever presses with short IRTs (IRTs < 1 s) by the number of responses with long IRTs (IRTs > 1 s). This is a conservative estimate, as not every response with a long IRT is followed by a response with a short IRT. Calculation of this ratio reveals that the average number of lever presses with short IRTs in a burst was approximately twice as high in the SHR as in the controls.

Further research on the function of responses with short IRTs is needed to determine whether behavioral elements differ between the two strains and how shaping and maintenance of behavioral elements are related to reinforcer strength and characteristics of the delay-of-reinforcement gradient. Also, a complete protocol of the behavior for each animal should be recorded in order to see the dynamic changes produced by the reinforcement history and to make it possible to detect and analyze response bursts.

5.2. The length of the delay gradient in SHR

In both present experiments, there were no strain differences in rates of responding during long reinforcer delays suggesting that the delay gradients are equally long in SHR and controls. Further, in experiment 2, response rates during each reinforcer delay condition were compared to response rates during the schedule when reinforcers were presented independently of responding (VT). The underlying assumption for these analyses was that if response rates during VT and a particular reinforcer delay were not significantly different, then the operant level had been reached and the reinforcer no longer controlled the responding. Comparisons between VT and reinforcer delays for responses both within and outside the operant class (IRTs < 1 s and IRT > 1 s, respectively) across the three segments showed no systematical strain differences, indicating that the delay-of-reinforcement gradients are equally long in the two strains (Fig. 6).

An additional finding from testing the VT schedule was that rates of lever pressing and tray visits were significantly elevated in the SHR during the last segment of the five last sessions running the VT schedule (Fig. 5). The termination of the response–reinforcer contingency during the VT schedule may be viewed as an extinction procedure, and response output at the end of the session is an important indicator of the extinction process. Thus, the present findings support the prediction of an extinction deficit in the SHR [23,24,26,45]. However, whereas lever pressing was without consequences, tray visits were necessary for accessing the "free reinforcers". Thus, lever pressing and tray visits may be fundamentally different, and lever pressing may better illustrate the possible slower extinction process in SHR.

5.3. The steepness of the delay gradient in SHR

In both experiments, we found statistically significant strain by delay interaction effects suggesting a more rapid decrease of responding in the SHR compared to the controls as a function of reinforcer delay. However, estimates of the

parameter K in the hyperbolic equation produced inconsistent findings. Parameter K represents the decaying effect of the reinforcer as a function of delay and is an indirect measure of the steepness of the delay gradient. In experiment 1, there was no statistically significant strain difference in rate of decay although estimates of K were generally higher in the SHR than in the controls. The estimates of reinforcer decay were also in experiment 2 generally higher in SHR than in the controls. However, there were no significant strain differences in estimates of rates of reinforcer decay at the start of the sessions, but at the end of the sessions estimates of K were statistically significantly higher in the SHR than in the controls.

Assuming that reinforcers act on both single responses and on the temporal relation between responses even when no requirements to the IRTs are specified by the reinforcement contingencies, analyses of IRTs distributions may add important information to investigations of reinforcer effects. The selective reinforcement of IRTs may be determined by the shape of the delay gradient, e.g. a short and steep delay gradient may only reinforcer short IRTs.

The higher response rate during intermittent reinforcement and during no delay in SHR compared to controls consisted mainly of responses with short IRTs. The short IRTs were not present in the SHR at the start of the studies, but developed as a function of exposure to the reinforcement contingencies irrespective of whether short IRTs were a requirement of the reinforcement schedule or not. The increased rate of short IRTs in the SHR may be the result of a generally more potent total reinforcer effect generating a higher response rate; high rates of responses will produce shorter time intervals between responses and, hence, more short IRTs. In this perspective, the higher total reinforcer effect may be described by a generally higher delay gradient in SHR. Alternatively, a higher rate of responding may be produced by the selective reinforcement of responses with short IRTs. The higher response rate may primarily be caused by the steepness of the delay gradient imposing limitations to the reinforcement of IRTs, and not to generally a higher effect of the reinforcer (Fig. 6). In this perspective, the higher response rate is not caused by a generally higher delay gradient, but is caused by a steepened delay gradient mainly reinforcing short IRTs thereby producing a high response rate. Following these arguments, there may be two components contributing to total response output. The height of the delay gradient describing the general effect of the reinforcer, and a component determined by the steepness and length of the delay gradient affecting response rate through the reinforcement of IRTs.

Building on previous findings and the assumption that the delay gradients start at the same height in SHR and controls, the selective reinforcement of short IRTs in the SHR compared to in the controls found in the present study can be expressed as a steepened delay gradient in the SHR (Fig. 6). A steepened delay gradient will emphasize short IRTs relative to long IRTs as found in SHR responding, and may also contribute to the increased response rate in SHR compared to controls found during intermittent reinforcement. A steeper delay gradient in SHR is also consistent with the higher sensitivity to reinforcer delay in the SHR that was found in analyses of response rates in the present study. However, this interpretation is not fully consistent with estimates of reinforcer decay in the hyperbolic equation. The mean estimates of rate of decay were higher in the SHR than in the controls in both studies but this was not statistically significantly except during the last segment in the second study. It is possible that the study did not have sufficiently statistical power to reveal a strain difference in this parameter.

Also the development and maintenance of unnecessary tray visits changed systematically by reinforcer delay in both strains in the present experiments (Fig. 4). Tray visits were necessary for accessing the reinforcer, but were otherwise without consequence and may be termed “superstitious” behavior [54]. Changes in rates of tray visits as functions of reinforcer delays were surprisingly consistent across both experiments. Reinforcer delay of approximately 1 s generated the highest rate of tray visits in the SHR in both experiments, while the highest rate of tray visits in the controls was found for reinforcer delays of 3 and 4 s in experiments 1 and 2, respectively. This strain difference may be interpreted as an increased sensitivity to the temporal response–reinforcer relation in the SHR, consistent with the hypothesis of a steepened delay gradient compared to controls.

6. Summary and conclusion

In spite of the two experiments using different reinforcement schedules, they yielded closely similar results (Fig. 2). The fundamental behavioral properties were similar both when single lever presses as well as sequences of lever presses (bursts of lever presses with short IRTs) were reinforced. It is functionally significant that the fundamental behavioral relationships appear to be independent of whether a single response, or a sequence of responses, is the behavior specifically reinforced and maintained by the schedule. The highly consistent results from fitting the hyperbolic decay function to the behavioral data in the two experiments, explaining more than 90% of the variance, indicate that fundamental behavioral processes are being measured and modeled here. Also, the findings are in general agreement with a study of delayed reinforcers using intra-cranial self-stimulation in the SHR [25].

Combined with previous findings, the present results suggest that the delay gradients in SHR and controls start equally high and are equally long (Fig. 6). The selective reinforcer effect on responses with short IRTs in SHR relative to controls and the increased sensitivity to reinforcer delay in SHR is consistent with a steepened delay gradient in SHR relative to controls (Fig. 6). However, the estimates of the reinforcer decay parameter were inconsistent with a steepened delay gradient in SHR. The estimates of reinforcer decay were generally higher in SHR than in controls, but a statistically sig-

nificant difference in reinforcer decay was only found during the latter part of the second experiment.

The findings highlight important further issues; clarification of the role of short IRTs in the SHRs responding, whether the response element of the SHR differs from those of the controls, and, finally, how the findings relate to characteristics shape of the delay-of-reinforcement gradient and underlying neurobiological factors in the SHR.

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