A BRIEF OPPORTUNITY TO RUN DOES NOT FUNCTION AS A REINFORCER FOR MICE SELECTED FOR HIGH DAILY WHEEL-RUNNING RATES

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Mice from replicate lines, selectively bred based on high daily wheel-running rates, run more total revolutions and at higher average speeds than do mice from nonselected control lines. Based on this difference it was assumed that selected mice would find the opportunity to run in a wheel a more efficacious consequence. To assess this assumption within an operant paradigm, mice must be trained to make a response to produce the opportunity to run as a consequence. In the present study an autoshaping procedure was used to compare the acquisition of lever pressing reinforced by the opportunity to run for a brief opportunity (i.e., 90 s) between selected and control mice and then, using an operant procedure, the effect of the duration of the opportunity to run on lever pressing was assessed by varying reinforcer duration over values of 90 s, 30 min, and 90 s. The reinforcement schedule was a ratio schedule (FR 1 or VR 3). Results from the autoshaping phase showed that more control mice met a criterion of responses on 50% of trials. During the operant phase, when reinforcer duration was 90 s, almost all control, but few selected mice completed a session of 20 reinforcers; however, when reinforcer duration was increased to 30 min almost all selected and control mice completed a session of 20 reinforcers. Taken together, these results suggest that selective breeding based on wheel-running rates over 24 hr may have altered the motivational system in a way that reduces the reinforcing value of shorter running durations. The implications of this finding for these mice as a model for attention deficit hyperactivity disorder (ADHD) are discussed. It also is proposed that there may be an inherent trade-off in the motivational system for activities of short versus long duration.

Key words: artificial selection, experimental evolution, genetics, motivation, wheel-running reinforcement, ratio schedule, lever press, rats

Mice from four replicate lines that have been selectively bred for high daily wheel running (total revolutions on days 5+6 of a 6-day exposure) run more than individuals from their four randomly bred control lines (Swallow, Carter, & Garland, 1998). This difference in wheel-running rates, as much as 2.7-fold, arises primarily because selected mice run faster, not longer, than controls, especially for females (Girard, McAleer, Rhodes, & Garland, 2001; Rhodes, Gammie, & Garland, 2005; Rhodes, Hosack, Girard, Kelley, Mitchell, & Garland, 2001). Research with these mice suggests that selective breeding has altered the dopamine system in the nervous system that is implicated in reward–reinforcement processes. Specifically, mice from the selected lines react differently to drugs that alter dopamine function. Dopamine agonists (i.e., cocaine, methylphenidate, GBR 12909) that block a dopamine transporter protein decreased wheel running in selected female mice, but had no effect or increased running in control mice (Rhodes & Garland, 2003; Rhodes et al., 2001). Apomorphine, a direct dopamine agonist, decreased wheel running in both control and selected mice; however, a higher dose was required to reduce running in selected mice. Finally, two dopamine antagonists, raclopride and SCH 23390, decreased running in both selected and control mice; however, a higher dose of SCH 23390, which is specific to the D1 receptor subtype, was required to reduce running in selected mice (Rhodes & Garland, 2003). In contrast, no differences in behavioral effects on selected and control mice were observed for the serotonin agonist, fluoxetine (Rhodes et al., 2001) or the opiate antagonists, naloxone and naltrexone (Li, Rhodes, Girard, Gammie, & Garland, 2004).

Cumulatively, the pharmacological evidence led investigators to conclude that selective

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breeding reduced dopamine functioning in the nervous system and that as a result of this alteration ''High Runner mice are more motivated (via an altered dopamine system) than Control mice to seek the wheel-running reward'' (Rhodes et al., 2005, p. 443). In addition, when selected mice are denied access to wheels, after having access for 6 days, neural activity, as indexed by fos-immunoreactivity levels, increases in brain regions (e.g., Medial Prefrontal Cortex and Striatum) implicated in natural and drug reinforcement (Rhodes, Garland, & Gammie, 2003). Based on the results, Rhodes, Garland, et al., (2003, p. 1252) concluded that ''mice may have been selected to become addicted to wheel running.''

Behavioral, pharmacological, and neural activity differences between selected and control mice suggest that wheel running should be a more efficacious reinforcer for selected mice. Studies of wheel-running reinforcement involve making the opportunity to run for a brief period of time contingent upon another behavior such as a lever press (Belke, 1997; Belke & Heyman, 1994; Collier & Hirsch, 1971; Iversen, 1993; Kagan & Berkun, 1954). This approach is based on operant conditioning where the opportunity to run functions as a reinforcing consequence that strengthens and maintains the operant behavior (i.e., lever pressing). From a response-strength perspective, a parameter of the operant response, typically rate, is interpreted as an index of the reinforcing efficacy of the consequence (de Villiers & Herrnstein, 1976). The more efficacious the reinforcer, the higher the rate of running and responding for the opportunity to run (Belke, 1996, 2004; Belke & Heyman, 1994; Belke, Pierce, & Jensen, 2004), as well as the shorter the pause following the termination of an opportunity to run before the animal initiates responding (Belke, 1996, 2004, 2006).

A preliminary study undertaken to compare the efficacy of an opportunity to run for 60 s as a reinforcer in control and selected mice encountered an unexpected problem. In order to use an operant procedure to assess reinforcer efficacy, animals must be trained to make a response (e.g., lever press) that produces an opportunity to run as a consequence. The procedure used to train this behavior was the method of reinforcing successively closer approximations (i.e., shaping). Using this procedure, 13 of 16 control mice readily learned to press a lever that produced a 60-s opportunity to run; however, only about 3 of 15 selected mice were successfully trained. This difference suggested the possibility of a learning or motivational deficit in the selected mice (see also Rhodes, van Pragg, et al., 2003). A learning deficit might lead selected mice not to readily learn to press a lever that produced the opportunity to run, because of a difficulty associating the consequence with the response that produces it. If this were the case, then the learning deficit would not be specific to wheel running, but would apply across behaviors and consequences. In contrast, a motivational deficit would be specific to wheel running. If a brief opportunity to run is of insufficient value to acquire and maintain lever pressing, then pressing a lever that produced this consequence would not be readily acquired.

Consequently, the objective of the present study was to more systematically explore this difference in the acquisition of lever-pressing behavior that produced an opportunity to run between selected and control mice. Rather than using the method of successive approximations, an autoshaping procedure (Brown & Jenkins, 1968) was used to initially train lever pressing. This procedure can be more readily quantified in that the presentation of a lever is paired with the occurrence of an opportunity to run in a trial, and the number of trials to meet a criterion indicative of acquisition of lever pressing can be determined. Following this initial autoshaping procedure, the animals were subsequently exposed to an operant procedure in which the opportunity to run for 90 s was made contingent upon a lever press. Using this procedure, the opportunity to run was increased to 30 min and then subsequently returned to 90 s. The purpose of this manipulation of reinforcer duration was to determine if a longer reinforcer would be more effective than a shorter reinforcer with respect to maintaining lever pressing.

METHOD

Subjects

Thirty-two female laboratory house mice (*Mus domesticus*) from the 41st generation of an artificial (as opposed to natural) selection

experiment for high voluntary wheel running (Swallow et al., 1998) served as subjects. The original progenitors (base population) for the selection experiment were outbred, genetically variable Hsd:ICR house mice. In each generation, 10 pairs of mice were used to propagate four lines selected for high voluntary wheel running and four control lines that were bred randomly with respect to wheel running. At 21 days of age, offspring were weaned from the dam, weighed, and toe-clipped for individual identification. Animals were housed in groups of 4, by sex, until they were tested for wheel running beginning at approximately 6–8 weeks of age. Selection was based on the total number of revolutions averaged over days 5 and 6 of a 6-day test where animals had free access to a running wheel for 24 hr (Swallow et al., 1998). In the selected lines, the highest-running male and female from each family were chosen as breeders. In the control lines, a male and a female from each family were randomly chosen with respect to wheel running to serve as breeders.

In the present study, mice were weaned as usual at 21 days of age, housed in arbitrary same-sex groups of 4 per cage, and then experienced the 6-day wheel test (described above) in the University of California, Riverside laboratory. At the end of day 6, wheels were blocked and mice were allowed wheel access for 30 min each night, beginning 2 hr after lights off. This regimen continued for 6 days. Mice were weighed prior to initial wheel access on day 1, at the end of day 6, and finally at the end of day 12. Age on day 1 averaged 72.3 days (SD = 3.90, min = 63, max = 76).

Mice then were shipped by air to Mount Allison University, where they were housed in groups of 4 with 2 selected and 2 control mice in each polycarbonate cage (480 mm long by 270 mm wide by 220 mm high). The cages were located on racks in a holding room on a 12-hr light/dark cycle, lights on at 1900, maintained at approximately 21°C. Food (Prolab RMH 3000) and distilled water were available ad libitum throughout the study. Animals were weighed each day following the completion of an experimental session.

Apparatus

As in the selection experiment itself (see Swallow et al., 1998), Wahman-type activity wheels (1.12 m circumference, 357 mm diameter, 100 mm wide running surface of 10 mm mesh bounded by clear Plexiglas and stainless steel walls, Lafayette Instrument, Lafayette, Indiana) were used for the experimental sessions. The eight wheels were located in sound-attenuating shells equipped with fans to mask extraneous noise and to provide ventilation. Each was modified such that a solenoid-operated brake was attached to the base. When the solenoid was operated, a rubber tip attached to a metal shaft contacted the outer rim of the wheel and brought the wheel to a stop. Twenty-four V DC lights mounted on the wheel frame served to illuminate the interior of the wheel chamber. Revolutions were recorded by a microswitch attached to the wheel frame

A retractable mouse lever (Med Associates ENV-112) was mounted at the circular opening (7.5 cm diameter) of each wheel. Each lever was 15 mm wide and extended 7 mm into the chamber. When extended, the lever was 46 mm above the mesh at the base of the wheel chamber. The force required to generate a response was approximately 0.024 N. A yellow LED light (3 mm in diameter) was located 20 mm above each lever. A water bottle was attached to the wheel frame by Velcro fastener to provide the mice with access to water when mice were in the running wheel over an extended period of time (i.e., 23 hr), but was not normally present for sessions lasting less than 2 hr. Control of experimental events and recording of data were handled by a Borland Turbo Pascal 4.0 program run on IBM PC computers interfaced to the wheel through the parallel port.

Procedure

The initial phase at Mount Allison involved providing the mice with access to a running wheel for 23 hr to assess wheel running. Groups of 8 animals (4 selected and 4 control) were placed in running wheels at 0900 each day and removed from the running wheel at 0800 the following day. Successive sets of 8 animals were given the opportunity to run for 23 hr once every 4 days until each animal completed 10 days of running.

Autoshaping phase. Table 1 presents a summary of the three conditions conducted during this phase of the study. Autoshaping began with 10 sessions of 20 trials. An

Table 1

For the autoshaping phase, the number of sessions, number of trials per session, lever duration (s), presence of a stimulus light over the lever, the duration (s) of wheel access, intertrial interval duration (s), and onset of chamber lights during wheel access are provided. For the operant phase, the number of sessions, number of reinforcers per session, reinforcement schedule, and wheel-running reinforcer duration(s) are provided.

Autoshaping phase							
Condition	Sessions	Trials	Lever Duration (s)	Stimulus Light	Wheel Duration (s)	ITI (s)	Chamber Lights
1	10	20	10	No	90	85	Yes
2	5	20	10	Yes	90	85	Yes
3	10	10	10	Yes	180	170	Yes

Operant phase				
Condition	Sessions	Reinforcers	Schedule	Reinforcer Duration(s)
1	25	20	FR 1/VR 3	90
2	10	20	FR 1	1800
3	25	20	FR 1	90

autoshaping trial began with the illumination of the lights at the side of the wheel chamber (i.e., chamber lights) and the extension of the retractable lever for 10 s. After 10 s the lever retracted, the brake released, and the wheel was free to turn for 90 s. After 90 s, the brake was applied, the chamber lights were extinguished, and the 85-s intertrial interval (ITI) commenced. When the ITI elapsed, the next trial commenced with the illumination of the chamber lights and the extension of the lever. A lever press any time during the 10 s that the lever was extended released the brake and initiated the 90-s wheel-running period.

After 10 sessions (i.e., 200 trials), a stimulus light was installed 20 mm above the retractable lever in each wheel and the procedure was changed so that the onset of the chamber lights was no longer correlated with the extension of the lever. In the previous procedure, the onset of the chamber lights and the extension of the lever were both correlated with the occurrence of the wheel-running period. The stimulus light above the lever was also added to direct sign-tracking behavior toward the lever rather than toward the chamber lights. With the addition of the stimulus light, a trial commenced with the onset of the stimulus light and the extension of the lever. Unlike the previous procedure, the chamber lights were extinguished while the lever was extended. After 10 s, the stimulus light was extinguished, the lever retracted, the brake released, and the chamber lights illuminated. These changes also occurred whenever the lever was pressed. After 90 s, the brake was applied, the chamber lights extinguished, and the 85-s ITI commenced. This procedure remained in effect for five sessions (i.e., 100 trials).

After five sessions, the number of trials per session was reduced from 20 to 10, the duration of the ITI was lengthened to 170 s, and the duration of the wheel-running period was increased to 180 s. These changes were made because autoshaping occurs more rapidly with fewer trials (Papini & Dudley, 1993) and a longer ITI relative to the CS+ (Gibbon, Baldock, Locurto, Gold, & Terrace, 1977). All other aspects of the procedure remained the same. This procedure remained in effect for 10 sessions (i.e., 100 trials). During this autoshaping phase, if a mouse responded on at least 50% of the trials in a session, then its behavior was considered shaped.

Operant phase. Table 1 presents a summary of the conditions during this phase. Initially, the mice were placed on a fixed-ratio (FR) 1 schedule with a 90-s wheel-running reinforcer. That is, a single lever press produced the opportunity to run for 90 s. Each session terminated when either 20 wheel-running reinforcers were obtained or 1 hr elapsed, whichever came first. If a mouse obtained 20 reinforcers over three consecutive sessions, then the schedule was changed to a variable-ratio (VR 3) schedule (i.e., an average of three presses required to produce 90-s wheel-running reinforcer). The purpose of this change in reinforcement schedule from continuous to intermittent was to strengthen responding. This condition remained in effect for 25 sessions.

After 25 sessions, mice that had been shifted to the VR 3 schedule continued on this schedule while mice that had failed to complete 20 reinforcers over three consecutive sessions were given free access to the running wheel for a 1-hr period each day. Free access was provided to reestablish wheel running in mice that were not running or running very little during the previous condition because they did not or rarely pressed the lever. After 7 days, water bottles were attached to the wheels. All mice were placed on the FR 1 schedule with the duration of the wheel-running reinforcement period extended to 30 min (i.e., 1800 s). As before, a session terminated when 20 reinforcers were obtained. Eight animals were run each day and each animal had one session every 4 days. This condition remained in effect until all animals had completed 10 sessions. In the final condition, animals were returned to the FR 1 schedule with a 90-s wheel-running reinforcer. Sessions terminated after 20 reinforcers or 1 hr, whichever came first, and all mice were run each day. Water bottles remained in place during this last condition. This condition remained in effect for 25 sessions. Sessions commenced at 0900 (2hr after lights off) in both the autoshaping and operant phases.

The dependent measures varied across the different phases of the study. During the initial phase, wheel revolutions were recorded. In the autoshaping phase, the number of lever presses and wheel revolutions were recorded. In the operant phase, lever presses, time spent lever pressing (for VR 3 schedule only), postreinforcement pause (PRP) duration, revolutions, and session duration were recorded. Postreinforcement pause duration refers to the time between the termination of a reinforcer and the first lever press.

Statistical Analyses

As in previous studies of these replicate selected and control lines of mice, we used a mixed-model analysis of variance to compare the two linetypes. Linetype was considered a fixed effect and was judged relative to the random effect of replicate line (n = 4 selected and 4 control) nested within linetype, with 1 and 6 degrees of freedom. The MIXED procedure in SAS version 9.1 (SAS Institute, Cary, NC) was used to compute F ratios for hypothesis testing by restricted maximum likelihood (REML). For analysis of body mass, age was included as a covariate. For analysis of wheel running in Riverside, age and a measure of wheel ''torque'' (Collier, Hirsch, Levitsky, & Leshner, 1975) were used as covariates. For days 7–12, the amount of time granted wheel access varied somewhat about the intended mean of 30 min, so the actual time allowed also was used as a covariate. The statistical significance of variation among the replicate lines was tested by comparing the restricted log likelihoods of a model with line included as a random effect to that of a model without line; twice the difference in the log likelihoods was compared with χ^2 with 1 d.f. (critical value = 3.841). We also fitted models that allowed separate variances for the selected and control lines, but in no case did this yield a significant improvement to the model so they are not reported. The effect of line was never statistically significant (all ps > 0.5) for the Riverside measurements of wheel running. Therefore, analyses of the data obtained at Mount Allison were performed with simple t-tests, ANOVA and χ^2.

RESULTS

Figure 1 depicts wheel-running rates (revolutions/hr) for the selected and control mice over three different intervals of access (30 min, 23 hr, and 24 hr) assessed in two different labs (University of California, Riverside and Mount Allison University). The depicted wheel-running rates were based on the number of revolutions for the selected and control mice for each animal on the last of 6 days of the 24-hr and 30-min wheel access conditions at the U of C, Riverside lab (Table 3) and the last 2 days of the 23-hr wheel access condition at Mount Allison (Table 3). Note that the wheel-running rate for the 30-min access period is much higher than those for the 23-hr and 24-hr access periods because it does not contain time periods (many hours) during which the animal would be quiescent (i.e., sleeping). Across different access periods and locations, mice selectively bred for high wheel-running rates ran at a higher rate than randomly bred control mice.

Table 2 shows mean total wheel revolutions during the 6 days of 24-hr access and 6 days of 30-min access for selected and control mice as

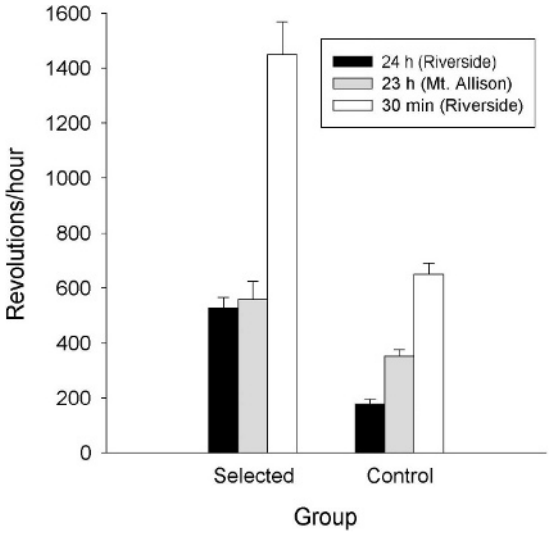

Fig. 1. Mean wheel running rates (revolutions/hr) for selected and control mice for the last days with 24-hr and 30-min access to a wheel at the University of California, Riverside laboratory and averaged over the last 2 days of 23-hr wheel access at the Mount Allison University laboratory. Ratios of revolutions for selected to control mice were about 3.1, 2.3, and 1.6 for 24 hr, 23 hr, and 30 min, respectively. Error bars represent ±1 SE.

well as the results of statistical analyses comparing the two groups, day by day, across both access conditions. When tested during the 24-hr access procedure in Riverside, mice from selected lines ran, on average, about 3.1-fold more revolutions/day as compared with the control lines. Over the following 6 days when given only 30 min of wheel access at night, selected mice still ran more than controls, although the fold difference was reduced to about 2.3. Table 3 shows the wheel revolutions for each animal on the last day of the 24-hr and 30-min access conditions, respectively.

Table 2 also reports body mass (g) at the start and end of the 24-hr access period as well as the end of the 30-min access period. As reported previously for these lines, selected mice were significantly smaller in body mass. Replicate lines varied in body mass, with p values of 0.0677, 0.0442, and 0.0196 for days 1, 6, and 12, respectively. Table 3 shows the mass for each animal prior to being given 24-hr access to a running wheel.

At Mount Allison, a comparison of the average number of wheel revolutions over the last 2 days of the 23-hr wheel access condition (Table 3) showed, as expected, that

Table 2

Wheel running (revolutions) and body mass (g) of 32 female mice when tested as part of the routine selective breeding protocol (days 1–6) and over a subsequent 6 days with time-constrained wheel access. Values are least-squares (adjusted) means and standard errors from SAS Procedure Mixed (for covariates used in analyses, see Method section).

Trait	Selected	S.E.	Control	S.E.	Selected/Control	p
24-Hour Wheel Access						
Day 1	6,797	644.9	2,513	644.9	2.70	0.0038
Day 2	8,727	746.8	3,397	746.8	2.57	0.0027
Day 3	11,579	908.0	3,917	908.0	2.96	0.0012
Day 4	14,251	799.7	3,740	799.7	3.81	0.0001
Day 5	14,028	702.1	3,944	702.1	3.56	<.0001
Day 6	12,708	728.8	4,223	728.8	3.01	0.0002
30-Minute Wheel Access						
Day 7	710	47.6	308	46.3	2.31	0.0011
Day 8	627	39.1	260	39.1	2.41	0.0007
Day 9	706	35.2	297	35.2	2.38	0.0002
Day 10	751	42.8	351	42.8	2.14	0.0008
Day 11	677	33.4	315	33.4	2.15	0.0003
Day 12	725	44.3	325	44.3	2.23	0.0008
Body Mass (g)						
Start of Day 1	23.45	0.992	27.33	0.992	0.858	0.0332
End of Day 6	23.40	0.859	26.62	0.859	0.879	0.0388
Change from Day 1–6	−0.03	0.355	−0.73	0.355	0.041	0.2205
End of Day 12	22.22	0.954	26.49	0.954	0.839	0.0197

Table 3

Mass (g) prior to being given access to a wheel, revolutions on the last day of 24-hr access, revolutions on the last day of 30-min access, and average revolutions over the last 2 days of 23-hr access for each control and selected mouse.

Control					Selected			
Mouse	Mass	24 hr	30 min	23 hr	Mouse	Mass	24 hr	30 min	23 hr
A2	25.0	7509	279	8921	A0	22.2	12125	926	17430
A3	33.5	4478	287	8927	A1	20.5	20785	944	7558
B2	29.3	4216	376	7103	B0	24.7	14516	707	5763
B3	32.5	3191	255	7007	B1	24.3	7293	731	7355
C0	28.7	5893	363	7724	C2	22.7	14458	596	18321
C1	22.9	3114	138	7052	C3	22.9	13695	708	12495
D0	31.2	3350	413	5210	D2	21.3	18509	875	22933
D1	27.8	4850	450	9957	D3	23.2	11691	741	4396
E2	24.4	4854	327	8572	E0	24.2	14692	629	16362
E3	26.9	5945	310	9407	E1	23.4	13293	1023	16491
F2	27.0	4127	399	12545	F0	25.2	9058	815	16101
F3	25.5	2344	248	4274	F1	20.5	10787	424	–
G0	29.6	3418	440	7314	G2	21.8	7354	376	6003
G1	23.9	7121	305	10961	G3	27.8	10579	937	10744
H0	24.7	668	313	6338	H2	22.8	12956	981	20558
H1	26.6	3108	300	8538	H3	25.5	10919	187	10108

the selected mice ran more than control mice, $t(17) = 2.94$, $p < .005$, one-tailed. On average, selected mice ran 12,841 (range 4,396 to 22,933) revolutions compared to 8,115 revolutions (range 4,274 to 12,545) for control mice. When revolutions per 23 hr were broken down by running wheel, selected mice ran, on average, more revolutions than controls in seven of the eight running wheels. In the remaining wheel, there was only one selected mouse due to the death (unknown causes) of the other selected mouse (F1) during this initial phase.

By the end of the autoshaping phase, more control mice had met the criterion of pressing the lever on 50% of the trials in a session, χ^2 (1,31) = 4.21, $p < .05$. Only 1 of 15 selected mice met the criterion compared to 6 of 16 control mice (Table 4). In terms of when the criterion was met, 1 selected and 2 control mice met the criterion during the first condition. Another 4 control mice met the criterion during the second condition and 1 additional control mouse (C1) met the criterion during the third condition. This final mouse responded on 9 of the 10 trials in this final condition.

With respect to wheel running, control mice ran more revolutions than selected, $t(21) = -2.13$, $p < .05$, two-tailed. Selected and control mice ran an average of 271.17 (S.D. = 188) and 387.69 (S.D. = 101.5) revolutions per 30 min of cumulative access time (10 × 180 s), respectively, over the final 2 days of the last condition. Despite being provided brief opportunities to run, 2 selected mice, A1 and D3, did not run. D3 had an average of 0 revolutions. Casual observation revealed that this mouse tended to circle at the base of the wheel throughout the session. A1 ran three revolutions on one day and zero on the other. With these 2 mice removed from the analysis, the significant difference in revolutions favoring the control mice disappeared, $t(19) = -1.43$, ns.

When the mice then were placed on the FR 1 schedule with a 90-s reinforcer, all the mice that met the criterion during the autoshaping phase (with the exception of 1 control mouse) obtained 20 reinforcers in less than 1 hr in the first session. Mouse B2, the exception, obtained 17 reinforcers. In addition, 2 control mice that did not meet the criterion during the autoshaping phase obtained 20 reinforcers during this first session. None of the selected mice other than the one that met the criterion obtained 20 reinforcers.

The left panel of Figure 2 shows the percentage of selected and control mice that obtained 20 reinforcers in less than 1 hr during the last session of this condition. Significantly more control mice completed a session relative to selected mice, χ^2 (1,31) = 17.39, $p < .001$. Not all mice were on the

Table 4

Average number of lever presses and revolutions from the last two sessions of the third autoshaping condition. In addition, the maximum number of lever presses made during an autoshaping session is shown in parentheses, and mice that met a criterion of lever presses on 50% of trials in a session are denoted with an asterisk.

Control			Selected		
Mouse	Presses	Revs	Mouse	Presses	Revs
A2	0.0 (1)	480.5	A0*	2.5 (13)	465.0
A3*	6.5 (14)	412.0	A1	0.0 (0)	1.5
B2*	8.5 (16)	381.5	B0	0.0 (0)	94.0
B3	0.0 (3)	95.0	B1	0.0 (1)	172.5
C0*	9.5 (18)	426.0	C2	0.0 (0)	446.0
C1*	7.5 (9)	302.0	C3	0.0 (1)	575.5
D0	0.0 (1)	390.5	D2	0.0 (4)	453.0
D1	0.5 (1)	433.5	D3	0.0 (0)	0
E2	0.0 (2)	467.5	E0	0.5 (8)	98.0
E3*	0.0 (10)	378.5	E1	0.0 (1)	282.0
F2	4.0 (4)	466.0	F0	0.0 (1)	332.5
F3	0.5 (3)	354.5	F1	- -	-
G0*	9.5 (20)	452.0	G2	0.0 (0)	99.5
G1	0.0 (3)	244.5	G3	0.0 (0)	214.0
H0	0.5 (2)	451.0	H2	0.0 (4)	370.0
H1	0.0 (1)	468.0	H3	0.0 (1)	463.5

same reinforcement schedule—12 control mice were on a VR 3 schedule compared to 4 selected mice, χ^2 (1,31) = 7.24, $p < .01$. Of these mice, 11 control, but only 1 selected mouse, obtained 20 reinforcers within 1 hr over each of the last five sessions (see Tables 5 and 6). The remaining mice, 4 control and 11 selected were on the FR 1 schedule. Of these mice, none obtained 20 reinforcers in each of the five sessions. One selected mouse obtained 20 reinforcers in one session. Two control mice obtained 20 reinforcers in two and three of the five sessions, respectively. Across all 25 sessions in this condition, 14 control mice compared to 7 selected mice obtained 20 reinforcers within 1 hr at least once, χ^2 (1,31) = 5.91, $p < .05$.

The middle panel of Figure 2 shows the percentage of mice completing 20 reinforcers on an FR 1 schedule when the reinforcer duration was increased to 30 min. The difference between the groups in the percentage of mice completing a session greatly diminished when reinforcer duration was increased to 30 min. In the last session under this condition (see Tables 5 and 6), 15 of 16 control mice compared to 12 of 15 selected mice obtained 20 reinforcers, χ^2 (1,31) = 1.30, ns. Of the mice that failed to obtain 20 reinforcers, the control mouse obtained 12 reinforcers and the selected mice obtained 12, 17, and 0 reinforcers. As noted previously, mouse D3 circled repetitively at the base of the wheel and did not press the lever. This circling behavior was only observed when the mouse was placed in the wheel.

A comparison of wheel revolutions from Tables 5 and 6 between the 12 selected and 15 control mice that obtained 20 reinforcers during the last session of this condition revealed no significant difference, $t(13)$ =

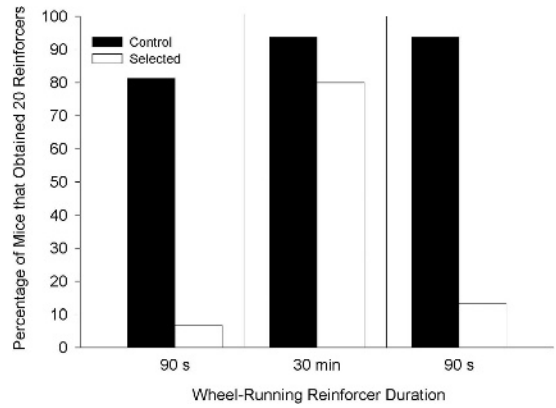

Fig. 2. The left, middle, and right panels show the percentages of control and selected mice that obtained all 20 reinforcers in the last sessions as a function of reinforcer duration on the FR1/VR 3 schedule 90-s reinforcer, FR 1 schedule 30-min reinforcer, and FR 1 schedule 90-s reinforcer conditions, respectively.

Table 5

Mean number of reinforcers obtained, mean number of revolutions, and median PRP over the last 5 sessions for the FR 1/VR 3 schedule 90-s reinforcer and FR 1 schedule 90-s reinforcer conditions, as well as the number of reinforcers obtained, revolutions, and median PRP in the last session of the FR 1 schedule 30-min reinforcer condition for the control mice. An asterisk indicates a mouse on a VR 3 schedule in the FR 1/VR 3 schedule 90-s reinforcer condition.

	FR 1/VR 3 90 s			FR1 30 min			FR 1 90 s		
Mouse	Reinf	Revs	Pause	Reinf	Revs	Pause	Reinf	Revs	Pause
A2	20.0*	433.2	12.8	20	7859	14.0	20.0	458.8	11.0
A3	20.0*	403.6	6.9	20	7433	13.8	20.0	388.2	7.6
B2	20.0*	415.0	5.4	20	6342	21.8	20.0	431.4	10.8
B3	8.0	101.0	13.5	20	5477	34.9	18.6	322.6	28.4
C0	20.0*	384.0	11.0	20	6561	11.7	20.0	403.6	10.3
C1	20.0*	289.6	13.6	20	4614	14.7	20.0	255.4	10.0
D0	18.8*	338.0	26.9	11	1325	2676.4	20.0	377.8	18.7
D1	0.0	0.0	0.0	20	5320	18.4	20.0	348.6	17.7
E2	20.0*	426.0	14.4	20	5651	21.0	20.0	421.4	24.2
E3	20.0*	456.2	8.6	20	7819	16.0	20.0	434.2	7.0
F2	20.0*	459.4	8.2	20	7568	15.2	20.0	467.4	16.3
F3	20.0*	468.8	15.8	20	5182	15.8	20.0	410.6	7.5
G0	20.0*	446.2	6.7	20	5678	7.9	20.0	450.6	6.2
G1	6.2	115.4	299.0	20	6263	314.7	5.4	86.2	186.5
H0	20.0*	387.4	17.3	20	4211	22.6	20.0	364.8	13.7
H1	12.0	228.8	14.6	20	5829	16.9	20.0	268.6	9.9

−.09, ns. Average revolutions per 10 hr of cumulative wheel access time for selected and control mice were 6,013.7 (S.E. = 1093.1) and 6,120.5 (S.E. = 295.5), respectively. However, PRP duration did differ. Tables 5 and 6 show the median PRPs from the distribution of PRPs in the last session for each control and selected mouse. Control mice paused for a shorter time following the termination of a reinforcer before they pressed the lever to produce the next reinforcer than did selected mice. Average median PRPs for the selected and control mice that obtained 20 reinforcers were 178.98 s (range 15.0 s to 945.1 s) and 37.29 s

Table 6

Mean number of reinforcers obtained, mean number of revolutions, and median PRP over the last 5 sessions for the FR 1/VR 3 schedule 90-s reinforcer and FR 1 schedule 90-s reinforcer conditions, as well as the number of reinforcers obtained, revolutions, and median PRP in the last session of the FR 1 schedule 30-min reinforcer condition for the selected mice. An asterisk indicates a mouse on a VR 3 schedule in the FR 1/VR 3 schedule 90-s reinforcer condition. For the FR 1 90-s reinforcer condition, the number of reinforcers obtained during the first session following the FR 1 30-min reinforcer condition is shown in parentheses.

	FR 1/VR 3 90 s			FR 1 30 min			FR 1 90 s		
Mouse	Reinf	Revs	Pause	Reinf	Revs	Pause	Reinf	Revs	Pause
A0	20.0*	507.8	21.0	20	13580	19.9	20.0 (20)	582.8	19.0
A1	0.0	0.0	0.0	12	402	4549.1	0.8 (2)	0.0	906.0
B0	4.0	61.2	78.4	20	500	324.9	1.2 (8)	5.2	1222.1
B1	0.6	7.0	699.4	20	3114	82.7	4.4 (5)	31.6	53.4
C2	0.4	5.8	2307.0	20	2503	945.1	2.0 (2)	21.2	94.5
C3	4.8*	116.8	51.3	20	3751	41.5	13.0 (20)	183.8	46.6
D2	3.4	44.8	39.6	20	8270	22.7	4.2 (20)	73.6	38.2
D3	0.0	0.0	0.0	0	0	0.0	0.0 (0)	0.0	0.0
E0	2.8	11.4	810.4	20	5014	302.5	4.6 (20)	39.0	197.3
E1	10.0	206.0	97.0	20	9203	264.0	9.4 (17)	141.8	103.2
F0	12.2*	221.0	54.2	20	3825	62.3	10.4 (13)	187.4	31.6
G2	0.0	0.0	0.0	20	5352	50.8	1.8 (11)	27.0	120.1
G3	0.2	4.8	759.7	17	2660	1773.1	2.0 (17)	20.4	276.7
H2	0.0	0.0	0.0	20	10773	16.4	5.0 (20)	76.2	137.2
H3	15.8*	399.0	14.6	20	6279	15.0	20.0 (20)	557.6	25.2

(range 7.9 s to 314.7 s), respectively. A Mann-Whitney U-test to compare ranks of median pause times between selected and control mice revealed that median pause times were significantly longer for selected mice, $U = 30$, $p < .01$. Although median PRPs differed between control and selected mice, time to first lever press at the commencement of a session did not, $U = 61.5$, ns. Median times to make the first response of a session for selected and control mice were 12.31 s (range 1.3 to 723.9 s) and 5.60 s (range 0.9 to 54.9 s), respectively.

Consistent with the difference in medians, total cumulative pause time was longer for selected than control mice. On average, cumulative PRP durations for selected and control mice were 15,146.8 s and 4,479.2 s, respectively. Since total cumulative PRP plus total wheel-running reinforcement time (i.e., 36,000 s) equals session duration, this difference in cumulative PRPs translated into longer session durations for selected mice. Average session times for selected and control mice were 51,146.8 s (14 hr 12.5 min) and 40,479.2 s (11 hr 14.5 min), respectively.

The right panel of Figure 2 shows the percentages of selected and control mice that obtained 20 reinforcers in 1 hr during the last session of the subsequent FR 1 schedule with a 90-s reinforcer condition. As was the case with the earlier 90-s reinforcer duration condition, almost all control mice (15 of 16), but very few selected mice (2 of 15) obtained 20 reinforcers, χ^2 (1,31) = 20.21, $p < .001$. Over the last five sessions (see Tables 5 and 6), 14 of 16 control mice obtained 20 reinforcers in 1 hr in every session compared to 2 of 15 selected mice, χ^2 (1,31) = 17.05, $p < .001$. Of the remaining selected mice, 2 obtained 20 reinforcers in 1 hr in one of the five sessions whereas 1 of the remaining control mice obtained 20 reinforcers in three of the five sessions. Across all 25 sessions in this condition, all 16 control mice compared to 8 selected mice obtained 20 reinforcers within 1 hr at least once, χ^2 (1,31) = 9.64, $p < .005$.

Table 6 also shows that the change in the performance of the selected mice when the wheel-running reinforcer duration decreased was not immediate. During the last session on the 30-min reinforcer duration, selected mice, with the exception of D3, obtained an average of 19.2 reinforcers. During the first session on the subsequent 90-s reinforcer duration condition, these mice obtained an average of 13.9 reinforcers. By the last five sessions, the average number of obtained reinforcers decreased to 6.1, 6.5, 9.1, 7.9, and 5.7 reinforcers, respectively. Of particular importance is the observation that several mice (e.g., C3, D2, E0, H2, G3, and E1) that obtained most or all of the reinforcers in the first session, obtained markedly fewer by the end of the condition.

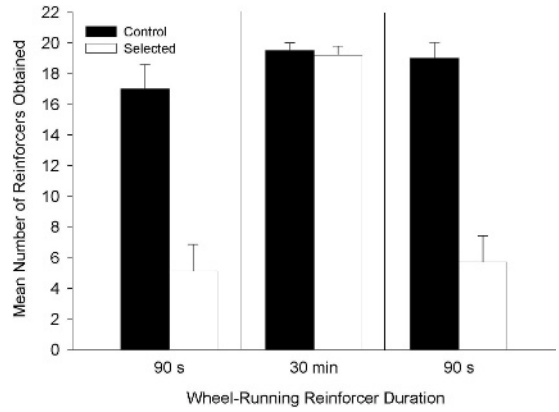

Fig. 3. The left, middle, and right panels show the mean number of reinforcers obtained in the last sessions on the FR1/VR 3 schedule 90-s reinforcer, FR 1 schedule 30-min reinforcer, and FR 1 schedule 90-s reinforcer conditions as a function of reinforcer duration, respectively. Note that data for mouse D3 is excluded from the calculation of the means for the selected mice. Error bars represent ±1 SE.

Figure 3 shows the mean number of reinforcers obtained by selected and control mice during the last session on the different reinforcer duration conditions. Note that data from the selected mouse D3 is not included in the average for the selected mice because this mouse failed to complete any reinforcers due to its behavior of circling within the wheel. Overall, the pattern parallels that for the percentage of mice completing a session. When the reinforcer duration was 90 s, selected mice obtained fewer reinforcers than when the reinforcer duration was 30 min. In contrast, control mice, on average, obtained almost all of the reinforcers within a session across the different reinforcer durations. A repeated-measures ANOVA with mouse type (Control, Selected) as the between-subjects factor and reinforcer duration (90 s, 30 min, 90 s) as the within-subject factor revealed significant main effects of mouse type,

$F(1,28) = 40.34$, $p < .001$, and reinforcer duration, $F(2,56) = 36.39$, $p < .001$, as well as a significant interaction, $F(2,56) = 23.25$, $p < .001$.

DISCUSSION

Mice from lines bred randomly with respect to wheel running (control lines) readily learned to press a lever to produce a brief opportunity to run, whereas few mice from the selectively bred lines did. During the autoshaping phase, more control mice met the criterion of responding on half of the trials in a session. On the operant contingency, responding was maintained by a brief opportunity to run in control, but not selected mice. When the opportunity to run was lengthened to 30 min, however, the difference between control and selected mice disappeared. Thus, both selected and control mice pressed a lever when it produced a 30-min opportunity to run. When reinforcer duration was subsequently returned to 90 s, selected mice that were pressing a lever when it produced a 30-min opportunity to run stopped pressing when a lever press only produced a 90-s opportunity to run.

Collectively, these data suggest that the difficulty that was encountered in the preliminary study with respect to training selected mice to press a lever to produce a brief opportunity to run was not due to a deficit in the ability to associate the behavior with a consequence (i.e., an association deficit), but may be attributable to the consequence being of insufficient value to acquire and maintain responding (i.e., a motivational deficit). Selected mice were more likely to respond and complete a session when reinforcer duration was 30 min than when it was 90 s. In contrast, control mice readily responded for the opportunity to run at both durations.

The observation that selected mice respond when the duration of the opportunity to run is longer may be related to the procedure used to select mice for breeding. Mice were selected as breeders based on wheel-running rates over 24 hr (more specifically, total revolutions on days 5 and 6 of a 6-day exposure to wheels). This selection procedure may have enhanced wheel running over extended periods of time; however, it may have come at the cost of diminishing the value of running over very brief periods of time. In other words, there may be an inherent trade-off in the motivational system for activities of short versus long duration. To our knowledge, this has not previously been suggested. If this is the case, then a reinforcer duration that more closely approximates the time period over which wheel running was genetically selected is likely to be a more effective reinforcing consequence than one that differs markedly from that time period. In this way, the effects of selective breeding on the wheel running and the motivational system related to wheel running may be akin to the selective effects of reinforcement contingencies on the distribution of gape sizes in pigeons (Deich, Allan, & Zeigler, 1988).

Investigating this difference between control and selected mice has potential implications for the experimental analysis of behavior and the nature of reinforcement. Altering the conditions under which a consequence functions as an effective reinforcer through selective breeding may further enhance our understanding of qualities that lead a consequence to function as a reinforcer. In particular, these data are relevant to theories of reinforcement that explain when, and under what conditions, an opportunity to engage in one behavior functions as a reinforcing consequence for another behavior (e.g., Premack principle, response deprivation, behavioral regulation) (Allison, 1993; Premack, 1959, 1965; Timberlake & Allison, 1974). For example, response deprivation theory would predict that an opportunity to run should function as a reinforcing consequence for lever pressing if wheel running is the more restricted behavior relative to its level of occurrence under unconstrained conditions. Unconstrained conditions would be the level of running with free access to a running wheel over 24 hr. On the schedule of reinforcement used in the current study, wheel running would have been the more constrained behavior relative to its baseline level and consequently, it should have functioned as a reinforcer for lever pressing. While this prediction holds for control mice, it does not hold for selected mice.

Alternatively, the constraint on wheel running could be viewed in terms of noncontingent versus contingent access to a brief opportunity to run. In this case, the autoshaping

procedure would represent unconstrained access to brief opportunities to run whereas the operant procedure with an FR 1 schedule would represent constrained access. From this perspective, selected mice (e.g., A1, B0, D3, E0, and G2) that did not run or ran very little when wheel access was noncontingent did not press for the opportunity to run when access was contingent. For these animals, a 90-s opportunity to run did not function as a reinforcer. However, a 90-s opportunity to run also did not function as an effective reinforcer for selected mice that ran at higher rates during the autoshaping phase (e.g., C2, C3, D2, E1, F0, G3, and H2). In contrast, for control mice (e.g., A3, B2, C0, C1, D0, E3, and F3) that ran at equivalent rates, a 90-s reinforcer did function as a reinforcer. Thus, the rate of running that occurred when access to brief periods of wheel running was noncontingent does not necessarily predict that a brief opportunity will function as a reinforcer when access is contingent upon another behavior.

Selectively breeding mice based upon rates of running over 24 hr may have altered the reinforcing value of wheel running in such a way that longer durations function as reinforcers, but shorter durations do not. One possibility is that selective breeding may have altered the relationship between duration and value. Killeen (1985) suggests that the relationship between duration and value can be described by the following equation:

$$v = c(1 - e^{-\lambda d}), \quad (1)$$

where v represents value of an incentive of duration *d*. Type or quality of reinforcement is represented by parameter *c*. λ determines the curvilinearity of the function relating value to duration. A small value of λ produces a linear function. As λ increases, the function becomes curvilinear and value increases rapidly to a maximum. With a large value of λ, the value of an alternative would reach an asymptotic level within seconds. If selective breeding reduced the value of λ, then value would increase very slowly with duration and reach an asymptote at a long duration. Consequently, with brief durations, the value of that opportunity to run would be insufficient to maintain responding. However, as durations lengthened, the value of an opportunity to run would increase to a level that would be sufficient to maintain lever pressing.

Similarly, longer durations might be required for selected mice to be able to run at a preferred speed (mice from the selected lines mainly run faster, rather than for more minutes per day, as compared with the control lines; Swallow et al., 1998; Girard et al., 2001; Rhodes & Garland, 2003). Shorter durations might not allow these higher rates. This suggests that the pattern of changes in wheel-running rates within an opportunity to run might differ between control and selected mice. Selected mice might run at lower rates initially and progressively increase their running rates. Future research should investigate within-wheel-running-period changes in wheel-running rates between selected and control mice for opportunities to run of different durations.

An apparent limitation of the current study is the lack of a control condition that measures the operant level of lever pressing prior to making the opportunity to run contingent upon lever pressing. The purpose of such a condition would be to demonstrate that an opportunity to run functioned as a reinforcer for both selected and control mice. That is, when the opportunity to run was contingent upon lever pressing on an FR 1 schedule, the rate or probability of lever pressing should be higher than the operant level. The absence of an assessment of the operant level of lever pressing raises the possibility that wheel running did not function as a reinforcer and that the differences in responding between selected and control mice on the FR 1 schedules leading to 90-s and 30-min opportunities to run might reflect a difference in operant levels of lever pressing. However, a couple of lines of evidence suggest that the opportunity to run did function as a reinforcer for lever pressing in control and selected mice. First, in the preliminary study, selected and control mice were shaped to lever press using the method of successive approximations with the opportunity to run for 60 s as the reinforcing consequence. Subsequently, the mice were trained on a VR 3 and a response-initiated variable-interval (VI) 5 s schedule. On the response-initiated VI 5-s schedule, the average local response rate for the 11 control mice that obtained 30 reinforcers in a 1-hr session was 27.7 presses/min (range 16.9 to 45.3 presses/min). The remain-

ing 2 control mice obtained only 17.8 and 17.5 reinforcers, on average. In comparison, only 1 selected mouse met this criterion of obtaining 30 reinforcers in a 1-hr session and its local rate of lever pressing was 16.4 presses/min. The remaining 2 selected mice obtained 10.4 and 14.2 reinforcers, on average. The mice that completed sessions on the response-initiated VI 5-s schedule were then placed on a progressive ratio schedule with an initial requirement of five responses, a step size of five responses, and a breakpoint criterion of 5 min without a lever press (not including PRP time). The reinforcer on this schedule was the opportunity to run for 3 min. Mean breakpoint values over the last 10 sessions on this schedule for the 11 control mice was 98.3 presses (range 23.5 to 188.0 presses) and 52.0 presses for the single selected mouse. These levels of responding support the contention that the opportunity to run functioned as a reinforcer.

Other evidence that supports the assertion that the opportunity to run functioned as a reinforcer, particularly for the selected mice, was the observation from the current study that most of the selected mice obtained more reinforcers during the first session on the FR 1 schedule with a 90-s reinforcer following the 30-min reinforcer. Several mice obtained all 20 reinforcers in less than 1 hr in this first session; however, by the last session, the number of reinforcers obtained by these mice decreased dramatically. If responding on the FR 1 schedule across these two reinforcer duration conditions was solely a function of an operant level of lever pressing, and wheel running did not function as a reinforcer, then it is difficult to account for the changes in responding that occurred between the first and the last session on the FR 1 90-s reinforcer condition. Instead, these data support the assertion that the change in responding across the different reinforcer durations reflects differences in the reinforcing value of the opportunities to run for the selected mice.

It is important to note, however, that although control and selected mice completed sessions when reinforcer duration was 30 min, session durations were longer for selected mice because they were taking longer to initiate responding following the termination of a reinforcement period. This difference could have arisen if selected mice required greater time to recover from a bout of running. Girard et al. (2001), however, showed that during peak nightly wheel running with 24 hr access, selected mice have shorter pauses between running bouts and more frequent bouts within a time period. This observation suggests that the PRP difference is probably not due to a difference in time of recovery following running. Another possibility is that the difference in PRP duration reflects a difference in motivation to initiate responding (Belke, 2006). If this is the case, then an opportunity to run was a more effective consequence for the control mice at both 90-s and 30-min reinforcer durations.

In addition there were two procedural differences between the 90-s and 30-min reinforcer durations that need to be considered. One is that there was a time limit for the completion of a session (i.e., 1 hr) when reinforcer duration was 90 s that was not in effect when reinforcer duration was 30 min. The other is that animals were tested every day when reinforcer duration was 90 s, but only once every 4 days when the duration was 30 min. These differences raise the possibility that selected mice would have obtained 20 short-duration reinforcers if the time limit was not in effect. Although this is possible, it seems unlikely because the average number of reinforcers among the selected mice that failed to complete 20 reinforcers within an hr was quite low. Control mice, in contrast, were readily able to obtain 20 reinforcers well within this time limit. Also, if the failure to complete sessions was a function of the time limit then one might expect that mice that had longer PRPs would obtain fewer reinforcers within the allotted time than mice with shorter PRPs. Although consistent with this prediction, the correlation was not statistically significant ($r = -.43$, ns, two-tailed) between the average number of reinforcers obtained over the last five sessions of the FR 1 90-s reinforcer condition, and median PRP duration from the last session of the FR 1 30-min reinforcer condition. Finally, the observation that a number of selected mice obtained 20 reinforcers within an hour in the first session of the second exposure to the 90-s reinforcer duration suggests that the time limit did not prevent selected mice from completing a session.

Investigating the difference between control and selected mice also is important because these selected lines may serve as an animal

model of attention deficit hyperactivity disorder (ADHD). The high-running mice share features in common with ADHD. First, they are hyperactive relative to nonselected mice, including when in cages without wheels (Rhodes et al., 2001). Second, Ritalin, which is widely used to treat ADHD, ameliorates hyperactivity in selected mice (Rhodes & Garland, 2003). Third, selected mice show a learning deficit relative to controls that may be a function of inattention (Rhodes et al., 2005). Specifically, high-runner mice housed with access to a running wheel for several weeks showed impaired spatial learning in a Morris water maze (Rhodes, van Praag, et al., 2003)—a task for which successful performance requires attention to visual stimuli. Fourth, reduced dopamine function and altered activity in the prefrontal cortex that occur in ADHD have been observed in selected mice (Rhodes et al., 2005).

With respect to reinforcement, results from the present study appear to be most consistent with Haenlein and Caul's (1987) theory that children with ADHD have an elevated reward threshold relative to normal children. ''The effect of this elevated reward threshold would be to decrease the magnitude of reward experienced for a given reinforcement by an ADDH [attention deficit disorder with hyperactivity] child compared with a normal child'' (Haenlein & Caul, 1987, p. 357). As a result, ''amounts of reinforcement large enough to sustain maximal performance in ADDH children would be well above the amount of reinforcement necessary to sustain maximal performance in normal children'' (p. 358). At lower levels of reinforcement, an amount of reinforcement sufficient to maintain responding in normal children would not sustain responding in ADDH children. If selective breeding based on high wheel running elevated the reward threshold for wheel running, then levels of running that would still function as reinforcers for control animals would no longer function as reinforcers for selected animals. However, differences in performance between control and selected animals should dissipate when the intensity and/or amount of reinforcement is increased.

In summary, a brief opportunity to run as a reinforcing consequence for lever pressing was not more effective in mice selectively bred based on high wheel-running rates and putatively addicted to wheel running. In comparison, randomly bred control mice readily responded for both brief and longer reinforcer durations. Selected mice only responded for an opportunity to run when it was of a longer duration. This suggests that a longer duration may be more effective as a reinforcer for the selected mice, but further investigation is required to determine why a brief opportunity to run does not function as an effective reinforcing consequence in high wheel running mice.

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