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Research report

Comparison of the validity of the use of the spontaneously hypertensive rat as a model of attention deficit hyperactivity disorder in males and females

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HIGHLIGHTS

- Female spontaneously hypertensive rats (SHR) have been much less studied than males.
- SHR rats are used to model symptoms of attention deficit hyperactivity disorder.
- We report that levels of impulsivity and hyperactivity are elevated in both sexes.
- However, only SHR males exhibit attentional deficits compared to same-sex controls.

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ABSTRACT

The spontaneously hypertensive rat (SHR) is a commonly used and well-studied rodent model of attention deficit hyperactivity disorder (ADHD). Sex differences in the cognitive symptoms of ADHD are reported. However, the female SHR rat is much less studied than its male counterpart. The goal of the current study was to assess the validity of the SHR rodent model of ADHD by examining attentional performance, inhibitory control, and hyperactivity in both male and female SHR rats. Adult SHR and control Wistar–Kyoto rats were trained on the 5-choice serial reaction time task, a self-paced test of attention and inhibitory control. This task requires animals to identify the location of a brief light stimulus among five possible locations under several challenging conditions. Analyses of percent correct revealed that attentional performance in SHR females was not significantly different from control females, whereas attentional performance in SHR males was significantly different from control males. Analyses of the number of premature responses revealed that SHR rats made more inhibitory control errors than did control rats and that this decrease in inhibitory control was present in both SHR males and females. Analyses of activity in the open field revealed that SHR rats were more hyperactive than were control rats and that this increased hyperactivity was present in both SHR males and females. The current findings have implications for the study of sex differences in ADHD and for the use of SHR rats as a model of ADHD in females.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is more frequently diagnosed in boys than it is in girls, with estimates typically ranging from 2:1 to 5:1 [1–3]. In 40–60% of children with ADHD, the disorder persists into adulthood [4], with a male:female ratio closer to 2:1 [5]. ADHD has a strong genetic basis [6] and is characterized by three core symptoms: attention deficits, pathological impulsivity, and extreme hyperactivity [7]. Studies investigating sex differences in ADHD indicate that females display greater attentional deficits and are more frequently diagnosed with the inattentive subtype of ADHD than are males [1,3], whereas males display greater inhibitory control deficits and are more frequently diagnosed with the hyperactive-impulsive and combined subtypes of ADHD than are females [8,9]. These findings suggest that males and females may differ in the way that they process attentional information [10]. Previous research using rodents supports this

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interpretation [11]. We have reported that female rats make more attentional errors than do males during challenging behavioral conditions and that male rats make more impulsive actions than do females when a delayed response is required [12]. In addition, male rats make more impulsive choices than do females for an immediate small food reward over a delayed large food reward [13].

ADHD affects 3–5% of the population [7], meaning that even with the sex bias in diagnosis, a significant number of females are diagnosed with ADHD. However, females are largely understudied with respect to preclinical research using animal models of ADHD [8]. Furthermore, the disparity in the diagnosis of ADHD and its subtypes between the sexes suggests that each sex expresses the disorder differently. Therefore, a greater understanding of the sex differences in ADHD can lead to novel insights into the etiology of the disorder. The spontaneously hypertensive rat (SHR) is one of the most commonly used and well-studied rodent models of ADHD [14]. However, the majority of studies conducted to validate the SHR model of ADHD have used only male animals [15–21]. SHR male rats exhibit deficits in attention, impulsivity, and hyperactivity, the three core symptoms of ADHD [14,22]. In addition, dopaminergic and noradrenergic neurotransmitter systems are hypofunctional in SHR male rats, similar to the neurochemical abnormalities observed in ADHD [14,16]. The few behavioral studies examining female SHR rats have focused on associative learning and conditioned inhibitory behavior [23–25]. These studies report that female SHR rats exhibit increased distractibility, less conditioned responding, and require more training sessions to learn an inhibitory response discrimination than do male SHR rats. Furthermore, gonadal hormone levels influence these sex differences in conditioned behavior. These studies were primarily designed to examine sex differences in SHR rats and not necessarily to validate the SHR model of ADHD in females through direct comparison to same-sex controls in a similar approach as the validation studies conducted using male animals. Furthermore, to our knowledge, no studies have investigated female SHR performance during tasks designed specifically to measure attentional performance.

One of the most commonly used tests of attentional performance and inhibitory control in rodents is the 5-choice serial reaction time task (5-CSRTT), which was developed from the continuous performance task used to quantify attentional deficits in humans [26]. During the 5-CSRTT, rats must identify the location of a brief light stimulus presented randomly across five possible locations over a large number of independent trials [27]. The 5-CSRTT has been shown to be dependent upon the prefrontal cortex [26] and assesses both attentional performance, the ability to continuously allocate attentional resources across many trials, and inhibitory control, the ability to refrain from making an inappropriate or premature response [28]. Only two studies to date have examined performance of male SHR rats on the 5-CSRTT. These studies provide inconsistent findings, reporting decreased attentional performance in male SHR rats as compared to controls [21], and reporting similar levels of attentional performance in SHR rats and controls [15]. To date, no study has examined the performance of female SHR rats on the 5-CSRTT.

The goal of the current study was to compare the validity of the SHR rodent model of ADHD in males and females by examining the three core symptoms of ADHD, attentional deficits, impulsivity, and hyperactivity, in SHR and same-sex control rats. In the current study as has been utilized in other SHR studies [18–20], we used the strain from which SHR rats were bred, Wistar-Kyoto (WKY) rats, as our control animals [29]. Attentional performance and inhibitory control in male and female SHR and control WKY rats were assessed on the 5-CSRTT under baseline conditions and under behavioral challenge conditions during which task difficulty was increased. Behavioral challenge conditions included shortening the stimulus duration, shortening the time before the onset of the stimulus, lengthening the time before the onset of the stimulus, and presenting a distracting noise. Following testing on the 5-CSRTT, activity levels were measured using the open field arena.

2. Materials and methods

2.1. Subjects

Eight male and eight female young adult SHR rats and eight male and eight female young adult control WKY rats, approximately 2 months of age, were purchased from Harlan Sprague Dawley Inc. (Indianapolis, IN). Animal care was in accordance with the guidelines set by the *National Institutes of Health Guide for the Care and Use of Laboratory Animals*, and all procedures were approved by the Institutional Animal Care and Use Committee of Tulane University. Animals were pair-housed under a 12-h light/dark cycle and tested during the light phase of the cycle. All animals were weighed daily following behavioral training and food was provided in their home cages to maintain their weights at 85% of their free-feeding weights while allowing for growth of approximately 2% of their body weight each week.

2.2. Testing on the 5-choice serial reaction time task

2.2.1. Apparatus

Animals were trained and tested in one of four separate 25 × 25 cm aluminum chambers (Lafayette Instrument Co., Lafayette, IN). The rear wall of each chamber was convexly curved and contained five light apertures, each 2.5 cm square, 4 cm deep, and set 2 cm above floor level. Each light aperture could be illuminated by a 3 W light bulb located at the rear of the hole, and each hole had an infrared photocell beam monitoring the entrance. The four conditioning chambers were individually housed in sound attenuating cabinets. Each chamber was illuminated by a 3 W house light and equipped with a speaker that could deliver bursts of white noise. The front wall could be opened to place in and remove the animal from the chamber. On the front wall, 25 cm from each nose-poke hole, there was a food magazine where 45 mg food pellets (Test Diet, Richmond, IN) could be automatically dispensed. Each animal received one session of training per day throughout the experiment. House lights were on unless stated otherwise.

2.2.2. Behavioral training

First, animals were successively shaped to retrieve food rewards from the food tray and to poke any of the holes to receive food rewards. Then each animal was trained daily for 30 min on the 5-CSRTT by passing through several training stages of increasing difficulty. Each session terminated after 100 trials had been completed or 30 min had expired, whichever occurred first. An animal was moved to the next training stage once it performed at >80% correct and <20% omissions for two consecutive days. Percent correct reflects the percentage of correct responses, whereas omissions reflect the failure to respond to the light stimulus. Each rat was always trained in the same conditioning chamber. Females were always trained in the same two chambers while males were always trained at the same time as the females in the other two chambers. Animals were trained at approximately the same time of the light phase each day.

For the initial training stage, animals were placed in the chamber and initiated the first trial by retrieving a single food pellet from the food tray. After a fixed 5 s intertrial interval (ITI), one of the five horizontal lights was illuminated for a maximum of 60 s (cue duration) or until a response had been made. From the time the light first turned on, the animal had 60 s (limited hold period) to respond by making a nose-poke into the previously lit aperture. Correct responses were immediately rewarded with delivery

of a food pellet into the food magazine, and retrieval of the food restarted the next trial after a 5 s ITI. Several types of errors were recorded: (i) responding into a non-lit aperture was recorded as an incorrect response; (ii) nose-pokes during the ITI were recorded as premature responses; and (iii) failure to respond within the limited hold period was recorded as an omission. All errors were punished by switching off the house light for a 5 s time-out period and no food was delivered. Responses to holes during this period would restart the time-out period.

For subsequent training stages, all parameters remained the same, but the stimulus duration was successively decreased from 60 to 1.5 s and the limited hold period was successively decreased from 60 to 5 s. For the final training stage (baseline training), the cue duration was further reduced to 1 s. Training with this protocol continued until all animals performed at a criterion of >70% correct with <20% omissions for five consecutive days.

2.2.3. Vaginal cytology

To control for effects of fluctuating ovarian hormones on performance, vaginal smears of female rats were collected by lavage each morning and analyzed daily beginning 2 weeks prior to behavioral testing. To control for handling effects, males underwent sham smears during which a small amount of water was placed on the genitals using a medicine dropper. Behavioral challenge conditions were only administered when a female was at the proestrus stage of the estrous cycle, at which time circulating estradiol levels are at their peak and vaginal cytology is characterized by large nucleated epithelial cells [30]. Each male was paired with a particular female and was always tested at the same time as that female.

2.2.4. Behavioral testing

The following series of manipulations to challenge performance were introduced for one daily session. To maintain performance on the task, animals received baseline training on all days in which rats were not at the proestrus stage. Therefore, rats received 3 days of baseline training between each behavioral challenge.

2.2.4.1. Baseline. Stimulus lasted for 1 s. A 5 s ITI was presented before onset of stimulus. Animal was given 5 s to respond before an omission was counted. Each session consisted of 100 trials. Rats were tested under baseline conditions until proestrus occurred. Data from this daily session was used for analysis. During each following proestrus, rats were tested under behavioral challenge conditions in the following order

2.2.4.2. Short stimulus. Stimulus duration was shortened from 1 to 0.5 s. All other parameters were the same as baseline. This condition challenges attentional performance because of the decrease in the duration of the stimuli.

2.2.4.3. Unpredictable short ITI. Time before the onset of the stimulus was pseudorandomly shortened to 1.5, 2.0, 3.0, or 4.5 s distributed across the 100 trials. All other parameters were the same as baseline. This condition challenges attentional performance because of the decrease in time between trials and the decrease in predictability of the stimuli.

2.2.4.4. Unpredictable long ITI. Time before the onset of the stimulus was pseudorandomly lengthened to 4.5, 5.5, 6.5, or 7.5 s distributed across the 100 trials. All other parameters were the same as baseline. This condition challenges attentional performance and inhibitory control because of the increase in time between trials and the decrease in predictability of the stimuli.

2.2.4.5. Distracting noise. Bursts of white noise (0.5 s, 85 dB, and 800 Hz) were presented at various time points during the 5-s ITI (0.5, 2.5, 3.5, or 4.5 s after start of the ITI). In 20% of the trials, no noise bursts were presented. All other parameters were the same as baseline. This condition challenges attentional performance because animals must maintain or refocus their attention to the stimuli following the burst of distracting noise.

2.2.5. Behavioral measures

Throughout testing, the following behavioral measures were recorded by automated computer software (ABET II, Lafayette Instruments) on a PC connected to the conditioning chambers.

2.2.5.1. Percent correct. This cumulative measure is the total number of correct responses relative to the total number of trials completed. It indicates overall attentional performance during the task where attention must be sustained and divided across several spatial locations.

2.2.5.2. Percent omissions. This cumulative measure is the percentage of trials in which a rat failed to respond during the limited hold period. This can reflect a failure to detect the stimulus due to inattentiveness or due to motivational and/or motor deficits. This distinction can be interpreted more conclusively by examining the speed measures. Following an omission, rats are punished by switching off the house light for a 5 s time-out period and no food is delivered.

2.2.5.3. Premature responses. This cumulative measure is the total number of trials in which a rat nose-poked into an aperture during the ITI. This reflects deficits in inhibitory control processes of response preparation. Following a premature response, rats are punished by switching off the house light for a 5 s time-out period and no food is delivered.

2.2.5.4. Perseverative responses. This cumulative measure is the total number of additional nose-pokes made into the apertures following either a correct or an incorrect response. This reflects inhibitory control processes of response control.

2.2.5.5. Speed. Two measures of speed were collected. First, the time between the onset of the stimulus and a correct nose-poke was measured as correct response latency. Second, the time between a correct nose-poke and the retrieval of the food from the magazine was measured as reward latency. Differences in response latency can indicate changes in decisional mechanisms, whereas differences in reward latency can indicate changes in motivational factors. If both measures are affected, motivational, and/or motor functions could be affected [26,31].

2.3. Testing on the open field arena

2.3.1. Apparatus and activity measurement

Testing was conducted in a black square open field arena. The environment measured 88 cm × 88 cm with walls that were 45 cm high. A camera placed above the arena recorded the movement of the rats. On the day of proestrus following the completion of 5-CSRTT testing, rats were placed individually into the open field maze for a 5 min testing period. Using camera tracking software, the arena was divided into 16 equally sized squares, and activity was measured as the total number of squares crossed.

2.4. Data analyses

In order to assess the validity of the SHR rat as a model of ADHD in each sex, male and female performance was analyzed separately. To assess the rate of acquisition of the task, the number of sessions before criterion performance was analyzed using a

one-way analysis of variance (ANOVA) with strain as the between-subjects factor. To assess the stability of baseline performance at the end of training, data across the last 5 days of training were analyzed using repeated measures ANOVAs for all dependent variables with day as the within-subjects factor. To assess possible changes in baseline performance resulting from behavioral challenge testing, data collected on the last 5 days of baseline training was compared to data collected the day before each behavioral challenge condition using repeated measures ANOVAs for all dependent variables with day as the within-subjects factor. To assess the disruptive effect of the behavioral challenges on performance, data collected during baseline testing on the day of proestrus in females prior to the first behavioral challenge and data collected during all behavioral challenge conditions (short stimulus, unpredictable short ITI, unpredictable long ITI, distracting noise) were analyzed for all dependent variables using repeated measures ANOVAs with behavioral condition as the within-subjects factor and strain as the between-subjects factor. To assess differences in activity levels during the open field activity testing, the total number of squares crossed was analyzed using a one-way ANOVA with strain as the between-subjects factor.

3. Results

One SHR female failed to reach criterion level performance during training and was excluded from behavioral testing, resulting in the following final group numbers: SHR male ($n = 8$), WKY male ($n = 8$), SHR female ($n = 7$), and WKY female ($n = 8$).

3.1. Baseline performance

Animals successfully acquired the task, as indicated by criterion level performance, within 60 training sessions. There were no significant strain differences in the number of sessions before criterion performance (mean ± SEM; female SHR: 49.86 sessions ± 3.49; female control: 44.00 sessions ± 2.64; male SHR: 47.5 sessions ± 2.57; and male control: 42.50 sessions ± 2.67). Performance remained stable across the last 5 days of baseline training. In addition, no significant changes in baseline performance occurred in males or females across the baseline sessions conducted in between behavioral challenge testing days.

3.2. Behavioral challenges

3.2.1. Percent correct

As illustrated in Fig. 1A and B, in both female and male rats there was a significant main effect of behavioral condition for percent correct (female: $F(4,52) = 11.69$, $p < 0.001$; male: $F(4,56) = 5.96$, $p < 0.001$), indicating that attentional performance was disrupted by the behavioral challenges in all groups. For male rats, there was a significant main effect of strain ($F(1,14) = 11.59$, $p = 0.004$), whereas there was no significant main effect of strain in female rats. There was no significant interaction between strain and behavioral condition for either sex. Results indicate that attentional performance was decreased in SHR males but not in SHR females as compared to same-sex WKY controls.

3.2.2. Percent omissions

As illustrated in Fig. 2A and B, in both female and male rats there was a significant main effect of behavioral condition for percent omissions (female: $F(4,52) = 8.58$, $p < 0.001$; male: $F(4,56) = 7.29$, $p < 0.001$), indicating that the number of trials omitted was impacted by the behavioral challenges in all groups. However, there was no significant main effect of strain or interaction between strain and behavioral condition for either sex, indicating that there was no effect of strain on the number of trials omitted.

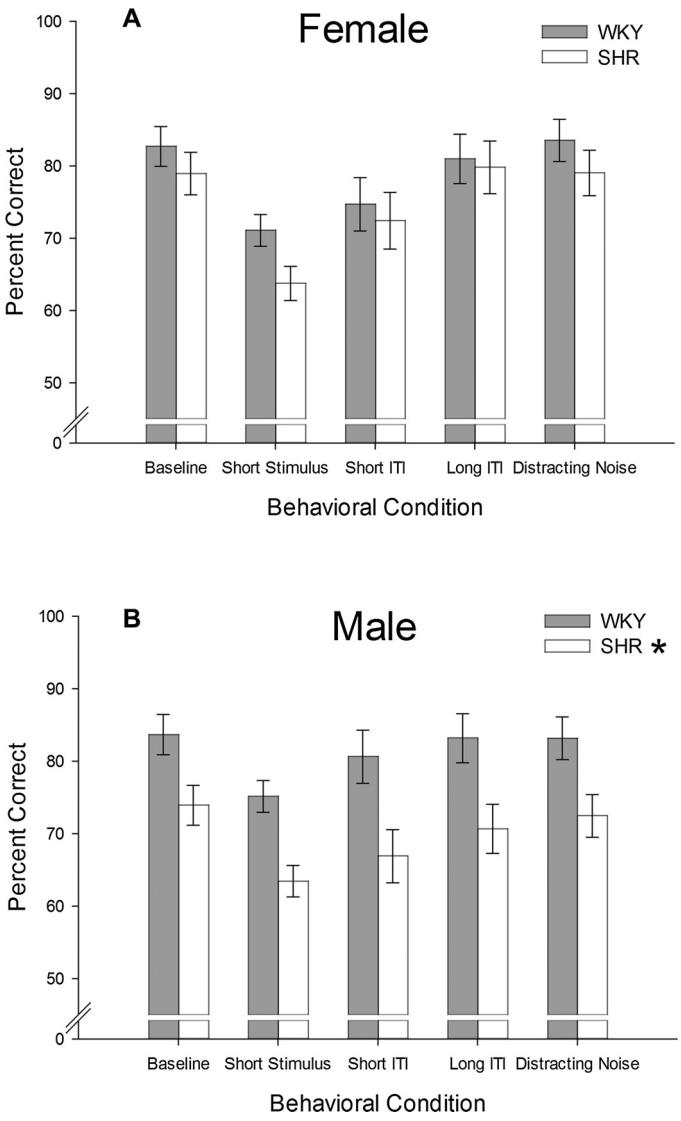


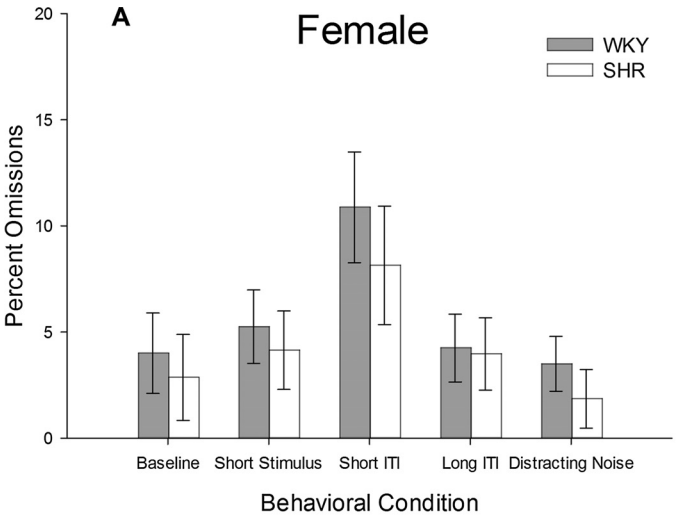
Fig. 1. Percent correct across behavioral condition in WKY control and spontaneously hypertensive (SHR) rats. A. Performance in females. No main effect of strain. B. Performance in males. Significant main effect of strain: * $p < 0.05$.

3.2.3. Premature responses

As illustrated in Fig. 3A and B, in both female and male rats there was a significant main effect of behavioral condition for premature responses (female: $F(4,52) = 18.72$, $p < 0.001$; male: $F(4,56) = 19.68$, $p < 0.001$), indicating that inhibitory control was disrupted by the behavioral challenges in all groups. For both female and male rats, there was a significant main effect of strain (female: $F(1,13) = 5.69$, $p = 0.033$; male: $F(1,14) = 10.70$, $p = 0.006$), indicating that inhibitory control was decreased in both SHR females and males as compared to same-sex WKY controls. There was no significant interaction between strain and behavioral condition for either sex.

3.2.4. Perseverative responses

In both female and male rats there was no significant main effect of behavioral condition, strain, or interactions between strain and behavioral condition for number of perseverative responses, indicating that the levels of unnecessary additional responding were



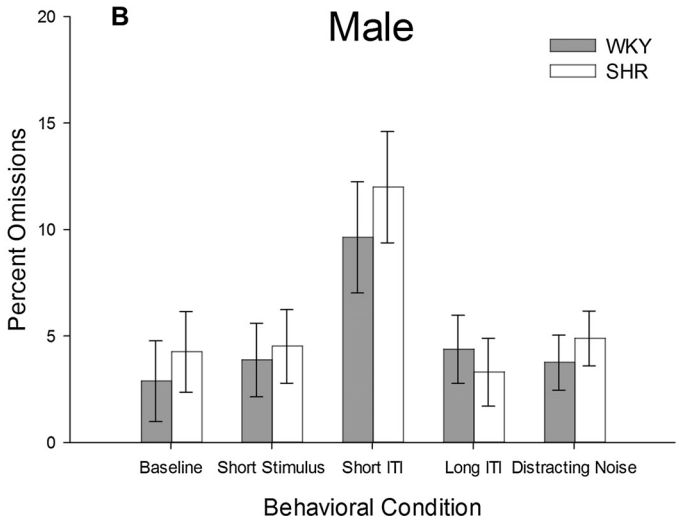
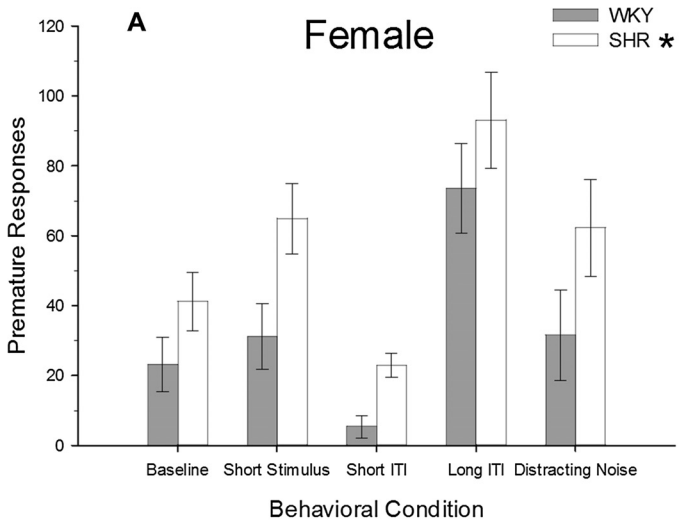


Fig. 2. Percent omissions across behavioral condition in WKY control and spontaneously hypertensive (SHR) rats. A. Performance in females. No main effect of strain. B. Performance in males. No main effect of strain.



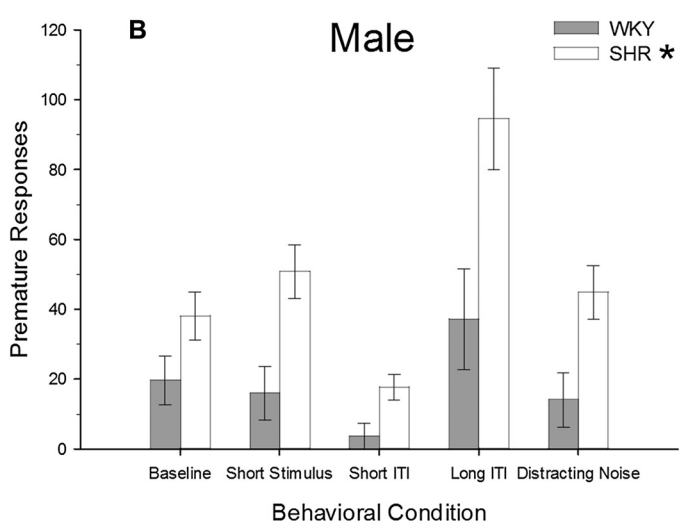


Fig. 3. Number of premature responses across behavioral condition in WKY control and spontaneously hypertensive (SHR) rats. A. Performance in females. Significant main effect of strain: * $p < 0.05$. B. Performance in males. Significant main effect of strain: * $p < 0.05$.

similar among SHR and same-sex WKY controls across the behavioral challenge conditions.

3.2.5. Speed measures

As illustrated in Table 1, in both female and male rats there were no significant main effects of behavioral condition, strain, or interactions between strain and behavioral condition for correct response latency. In addition, in both female and male rats there were no significant main effects of behavioral condition, strain, or interactions between strain and behavioral condition for reward collection latency. The similarity of the speed of task performance between groups indicates that there were no strain differences in motor function, sensory function, motivational factors, or the overall ability of the animals to perform the task during the behavioral challenges [26].

3.3. Open field activity

3.3.1. Total number of squares crossed

As illustrated in Fig. 4A and B, in both female and male rats there was a significant main effect of strain for total number of squares crossed (female: $F(1,13) = 31.64$, $p < 0.001$; male: $F(1,14) = 60.28$, $p < 0.001$), indicating that both SHR females and males were more active as compared to same-sex WKY controls.

4. Discussion

In the current study, we assessed the validity of the SHR rat as a model of ADHD by examining attentional performance, impulsivity, and hyperactivity in male and female SHR rats. The results demonstrate that attentional performance is decreased from that of same-sex controls in SHR male but not female rats. Male SHR rats performed with a significantly lower percentage of correct responses during baseline and behavioral challenge conditions on the 5-CSRTT as compared to same-sex control rats. No significant differences in the percentage of correct responses were discovered between female SHR and same-sex control rats during baseline and behavioral challenge conditions. The results also demonstrate that inhibitory control is decreased from that of same-sex controls in both SHR male and female rats. Both male and female SHR rats made more premature responses than did male and female control rats. Lastly, the results demonstrate that activity levels are

Table 1
Correct response latency and reward collection latency across behavioral challenge condition.

	Baseline		Short stimulus		Short ITI		Long ITI		Distracting noise	
	M	S.E.M.	M	S.E.M.	M	S.E.M.	M	S.E.M.	M	S.E.M.
Correct latency (s)										
Female SHR	0.69	0.04	0.71	0.04	0.62	0.03	0.70	0.05	0.66	0.03
Female control	0.71	0.04	0.72	0.04	0.67	0.03	0.70	0.05	0.71	0.03
Male SHR	0.69	0.04	0.70	0.04	0.63	0.03	0.67	0.05	0.67	0.03
Male control	0.69	0.04	0.70	0.04	0.63	0.03	0.67	0.05	0.68	0.03
Reward latency (s)										
Female SHR	1.02	0.04	0.98	0.04	0.96	0.04	0.99	0.05	0.99	0.05
Female control	0.99	0.04	0.99	0.04	1.01	0.04	1.01	0.05	1.10	0.05
Male SHR	0.98	0.04	0.99	0.04	0.97	0.04	0.96	0.05	1.00	0.05
Male control	1.03	0.04	1.00	0.04	1.01	0.04	1.03	0.05	0.97	0.05

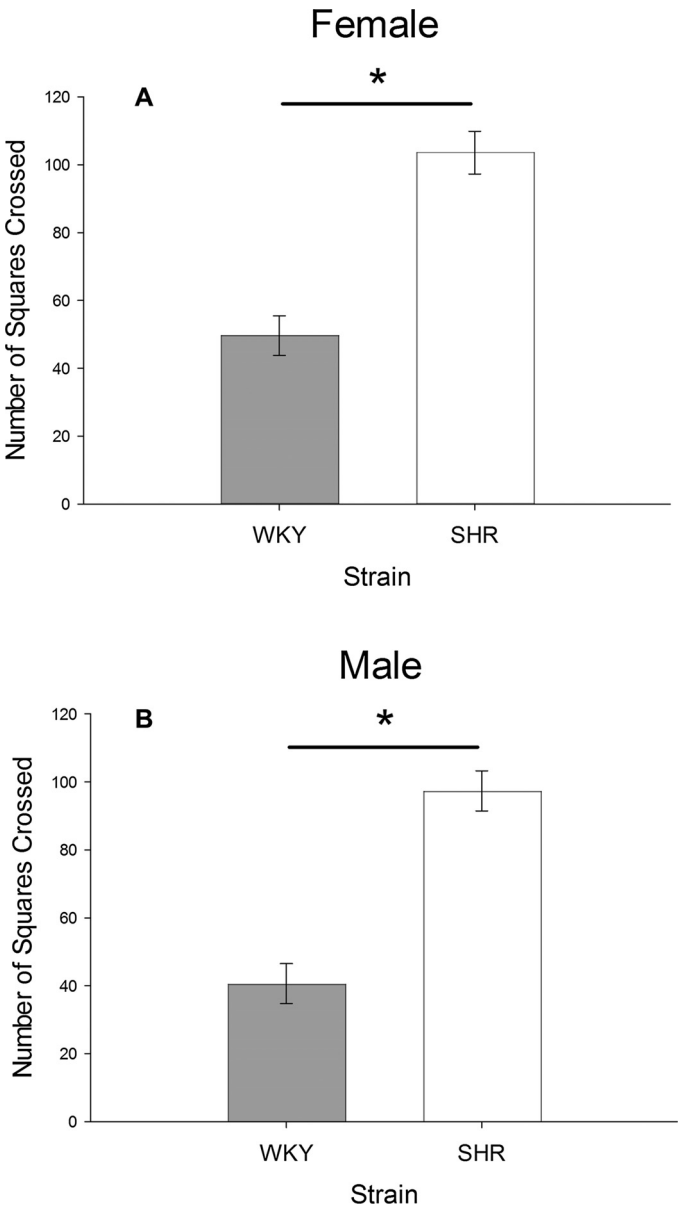


Fig. 4. Number of squares crossed during open field activity testing in WKY control and spontaneously hypertensive (SHR) rats. A. Performance in females. Significant main effect of strain: * $p < 0.05$. B. Performance in males. Significant main effect of strain: * $p < 0.05$.

increased from that of same-sex controls in both SHR male and female rats. Both male and female SHR rats made more crossings in the open field arena than did male and female control rats. Thus, our results demonstrate that the male SHR rat is well suited to model all three core behavioral deficits exhibited in ADHD, attentional deficits, impulsivity, and hyperactivity. However, while deficits in inhibitory control and hyperactivity are modeled well in the female SHR rat, deficits in attentional performance are not displayed in female SHR rats during performance of the 5-CSRTT.

In the current study, the strain differences during performance of the 5-CSRTT were consistent across behavioral challenge conditions. The behavioral challenge conditions were designed to alter attentional and inhibitory control demands in specific ways [26,27]. For example, the short stimulus condition decreases the event duration and the short and long ITI conditions alter both the event asynchrony and event rate. Interestingly, our analyses found no interaction between strain performance and behavioral challenge condition. That is, the challenging conditions affected SHR and control animals comparably. Furthermore, when a strain difference was discovered, it was detectable under baseline conditions suggesting a strong deficit in general attentional and inhibitory control processes in SHR rats as compared to same-sex controls. Additionally, in the current study, female animals were only tested during the proestrus stage of the estrous cycle, at which time circulating estradiol levels are at their peak [30]. We did so to control the effects of fluctuating hormone levels that occur across the estrous cycle. It remains to be determined if the current pattern of effects revealed under behavioral challenge conditions would be maintained during periods of low levels of circulating estradiol, such as are present during the diestrus phase of the cycle. However, analyses of baseline performance during the last 5 days of baseline testing and baseline testing in between behavioral challenge conditions revealed that individual group performance did not significantly vary across these days that included all of the stages of the estrous cycle.

The diagnosis of ADHD is behaviorally based, so ideally, a quality animal model would display the behaviors exhibited in the human disorder. In humans, both males and females with ADHD have difficulties focusing and maintaining their attention on a task [4,32]. The present study is the first study to utilize the 5-CSRTT to examine attentional performance in female SHR rats. Attentional performance was not significantly different in female SHR and same-sex control rats during baseline and behavioral challenge conditions. Studies investigating sex differences in ADHD indicate that females display greater attentional deficits and are more frequently diagnosed with the inattentive subtype of ADHD than are males [1,3]. Given that attentional deficits are the most commonly expressed symptom of ADHD in females, the current findings suggest that the female SHR rat may not be as useful of a model of the inattentive

symptoms of ADHD as is the male SHR rat. Male SHR rats made more attentional errors during performance of the 5-CSRTT than did same-sex controls. This deficit in attentional performance was consistent across baseline and all behavioral challenge conditions. These results are consistent with the previous study reporting an attentional deficit in male SHR performance on the 5-CSRTT [21] and in contrast to the previous study reporting no differences in attentional performance between male SHR and same-sex control rats [15]. In the latter study, attentional performance in male SHR rats was decreased, albeit insignificantly, from that of WKY control rats when tested under similar baseline conditions as in the current study. The criterion performance to be achieved prior to testing in that study was set at 60% correct as compared to 70% correct in the current study and 80% in the previous study reporting a deficit in male SHR attentional performance [21]. In the current study, the increased performance demands during baseline training, as well as the addition of the behavioral challenge conditions, may have reduced the variability in individual performance and increased the ability to detect a group difference in attentional performance.

In addition to attentional deficits, males and females with ADHD have trouble inhibiting inappropriate or premature behaviors [4,32]. Males with ADHD typically display greater inhibitory control deficits than do females [8,9]. However, both sexes display inhibitory control deficits compared to their same-sex peers in the general population [4,32]. The results of the present study support the use of the SHR rat as a model of the impulsive behaviors exhibited in ADHD. Male and female SHR rats made more impulsive premature responses than did control rats across baseline and all behavioral challenge conditions of the 5-CSRTT. Similar findings have been reported previously in the male SHR rat. Male SHR rats display motor impulsiveness by making significantly more responses with short inter-response times during fixed-interval/extinction schedules of reinforcement than do same-sex control rats [22], and male SHR rats exhibit more short runs without stopping or exploring their paths than do same-sex control rats [33,34]. However, no differences in impulsive responding between male SHR and same-sex control rats during baseline performance of the 5-CSRTT have previously been reported [15,21]. Our findings are in contrast to these findings. The addition of the behavioral challenges in the current study may have increased the demands on inhibitory control allowing for the detection of the effect of SHR strain on premature responding during the 5-CSRTT. A previous study examining sex differences reported that female SHR rats exhibited less conditioned responding and required more training sessions to learn an inhibitory response discrimination than did male SHR rats [23]. In the present study, female SHR rats learned to perform the 5-CSRTT at a similar rate as male SHR rats and impulsive responding increased in a similar pattern and magnitude in male and female SHR rats across the behavioral challenge conditions.

Males and females with ADHD also display high and uncontrollable levels of activity [4,32]. Our findings support the use of the SHR rat as a model of the hyperactive symptoms exhibited in ADHD. Male and female SHR rats were more active in the open field arena than were control rats. Studies indicate that female rodents are often more active than are males but that this sex difference can vary by age and strain [35]. Previous studies examining activity levels in SHR rats have yielded inconsistent results. For example, male SHR rats display increased hyperactivity levels during fixed-interval/extinction schedules of reinforcement [22]. However, in the open field arena, studies have reported no increase in hyperactivity levels in SHR rats as compared to same-sex controls [36] and elevated levels of hyperactivity at 30 days of age in male SHR rats but not female SHR rats as compared to same-sex controls [15]. Our findings indicate that activity levels are increased in both male and female young adult SHR rats as compared to same-sex controls, suggesting that the hyperactive symptoms of ADHD are modeled well in both sexes of the SHR rat at this age.

4.1. Conclusions

The current findings reveal that during performance of the 5-CSRTT male SHR rats commit significantly more inhibitory control errors, as measured by number of premature responses, and significantly more attentional errors, as measured by percent correct, than do same-sex WKY control rats. However, female SHR rats commit significantly more inhibitory control errors but do not commit significantly more attentional errors than do same-sex WKY control rats. During testing in the open field arena, both male and female SHR rats display hyperactivity as compared to same-sex WKY control rats. These results indicate that the male SHR rat is well suited to model all three core behavioral deficits exhibited in ADHD, attentional deficits, impulsivity, and hyperactivity. However, because a quality animal model of ADHD should demonstrate behavioral deficits in all three core symptoms of ADHD and no differences in attentional performance were observed between female SHR and same-sex control rats, the SHR animal model of ADHD may not be as useful in understanding the behavioral and biological characteristics of ADHD in females as it is in males.

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