Effects of methylphenidate on impulsive choice and delay aversion in Lewis rats
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Attention-deficit/hyperactivity disorder (ADHD), a common behavioral disorder in children and young adults, is characterized by symptoms of impulsivity, inattention, and hyperactivity. The purpose of this study was to evaluate the Lewis rat strain as a model of ADHD by testing their impulsive choices. Lewis rats were compared to their source strain, the Wistar rat, on an impulsive choice task. Rats completed the tasks on and off methylphenidate, a commonly prescribed medication for ADHD. Off methylphenidate, Lewis rats made more impulsive choices than Wistar rats. Analyses of acquisition of choice behavior suggested that both strains were able to discriminate reward sizes, but Lewis rats still chose the smaller-sooner option more than the larger-later (LL) option when the delays to reward were the same. This may be due to an aversion to the LL lever, which was associated with the longest delays to reward. Higher doses of methylphenidate increased LL choices in Lewis rats but decreased LL choices in Wistar rats. Altogether, these results suggest Lewis rats may be a viable model for ADHD in individuals whose symptoms are characterized by impulsive choices. Behavioural Pharmacology 34:169–178 Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction
Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder typically characterized by problems with attention, hyperactivity, and impulsivity (Castellanos and Tannock, 2002; Tarver et al., 2014). Clinicians recognize three main subtypes or presentations of Diagnostic and Statistical Manual of Mental Disorders (ADHD; APA, 1994; Epstein and Loren, 2013) – predominately inattentive, predominantly hyperactive-impulsive, or combined. Subtypes of ADHD may relate to differing underlying psychological constructs. For example, Sonuga-Barke (2002) proposed that the combined subtype of ADHD may be described both psychologically and neurobiologically in a dual pathway model. The two paths are poor inhibitory control, or the inability to stop an initial impulse, and delay aversion, or the subjective dislike of waiting. The first pathway suggests that ADHD may be the result of dysregulation of action in the mesocortical dopaminergic circuitry, culminating in poor inhibitory control. The second pathway suggests that ADHD may be caused by altered motivation in mesolimbic dopaminergic circuitry, resulting in delay aversion. Altogether, diagnostic subtypes of ADHD may be characterized by both symptoms and psychological constructs.

The most commonly prescribed medication to children and adults for ADHD is methylphenidate, which increases dopamine and norepinephrine in the synaptic cleft by blocking reuptake (Volkow et al., 2001, 2002; Castellanos and Tannock, 2002; Askenasy et al., 2007; Tarver et al., 2014). Methylphenidate effectively reduces symptoms in children and adults with ADHD (Pliszka, 2007; Kolar et al., 2008). However, the exact mechanism of action by which methylphenidate produces these therapeutic effects is still poorly understood.

Ideally, an animal model of ADHD should demonstrate all symptoms and show improvements with methylphenidate, displaying face and construct validity. Spontaneously hypertensive (SHR) rats have been proposed as an animal model of ADHD because they exhibit higher levels of attentional deficits, hyperactivity, and impulsivity compared to control strains (e.g. Bizot et al., 2007; Fox et al., 2008; see Sagvolden, 2000 for a review). The SHR strain has been reported as more impulsive on two-option, fixed-time impulsive choice tasks compared to Wistar-Kyoto and Wistar control strains in some studies (Bizot et al., 2007; Fox et al., 2008; Sagvolden et al., 2009), but other studies have not found this result using a two-option, fixed-interval impulsive choice task (Garcia and Kirkpatrick, 2013). The fixed-time tasks do not require a response to collect the reward, whereas the fixed-interval tasks do require a reward collection response, and thus may engage attention more effectively. More recently, SHRs were compared to the Wistar strain on measures of inhibitory control and impulsive choice with both positive and negative consequences delivered in the form of food rewards with and without electric
Another potential test of the validity of an animal model is the response to methylphenidate. The response of SHRs to methylphenidate is mixed. In some instances, methylphenidate reduced impulsive choices (Slezak and Anderson, 2011), but other studies have not replicated this effect (Bizot et al., 2007; Wooters and Bardo, 2011). While these experiments offered choices between smaller-sooner (SS) and larger-later (LL) options, they differed in reward amounts associated with each choice, which may account for the discrepancy. Overall, methylphenidate does not reliably improve impulsive choices in SHRs unlike what is observed in humans. The behavioral deficits observed in SHRs may be a result of a different mechanism than that of children and adults with ADHD, which are typically improved by methylphenidate. Taken together, these studies suggest that the SHR strain may not be a comprehensive model for ADHD, and other strains should be examined for response to methylphenidate.

Another potential animal model of ADHD is the Lewis rat strain. Garcia and Kirkpatrick (2013) demonstrated that Lewis rats were significantly more impulsive than their source strain, Wistar rats. Lewis rats made more impulsive choices when both the delay and magnitude of reward were changed in an impulsive choice task, suggesting that the Lewis strain may be a model for the impulsive choice component of ADHD. Other studies have demonstrated that Lewis rats exhibit greater impulsive choices than Fischer 344 rats (another inbred strain) across several impulsive choice tasks (Anderson and Woolverton, 2005; Madden et al., 2008; Anderson and Diller, 2010; Huskinson and Anderson, 2012; Huskinson et al., 2012). Lewis rats also show deficits in inhibitory control measured on the five-choice serial reaction time task (Hamilton et al., 2014). This suggests that the Lewis rats demonstrate psychological constructs relevant to both pathways within the dual pathway model of ADHD (Sonuga-Barke, 2002).

Overall, Lewis rats may be a viable model of the hyperactive-impulsive subtype of ADHD. However, as noted earlier, the response to methylphenidate is an important validation check for animal models. Further research is needed to assess the effects of methylphenidate on Lewis rats’ impulsive choices. If the Lewis rat is a viable model for ADHD, then methylphenidate should normalize impulsive choice as in humans. The goal of this experiment is to measure impulsive choice in Lewis rats and investigate the effects of methylphenidate on choice behavior. Lewis rats should make more impulsive choices than Wistars (their outbred source strain), and methylphenidate should increase self-controlled choices in Lewis rats, similar to the effects produced when methylphenidate is administered to children and adults with ADHD (Pliszka, 2007; Kolar et al., 2008).

**Methods**

**Subjects**

The experiment consisted of 24 experimentally naive male Lewis ($n = 12$) and Wistar ($n = 12$) rats sourced from Charles River (Lewis strain: Kingston, New York, USA; Wistar strain: Raleigh, North Carolina, USA). Although rats were sourced from different facilities, they arrived in the same shipment at the animal facility (Kansas State University, Manhattan, Kansas, USA) at 21 days of age. The number of rats used in the current study was determined by referencing published research with similar research designs. Rats were pair-housed under a reverse 12-h light:dark cycle (lights off at 7 a.m.). Ad libitum water was available in the home cages, and the rats were fed daily with standard rat chow to maintain approximately 85% of their projected ad libitum weight based on growth curves obtained from the supplier. Rats were fed in their home cages after behavioral testing at approximately 3:30–4:30 p.m. Treatment of the rodents was conducted in compliance with American Psychological Association ethical standards and Institutional Animal Care and Use Committee ethical standards.

**Apparatus**

Twenty-four operant chambers (Med-Associates, St. Albans, Vermont, USA), each housed within a sound-attenuating, ventilated box ($74 \times 38 \times 60$ cm), were used to conduct this experiment. Each operant chamber ($25 \times 30 \times 30$ cm) was equipped with a stainless-steel grate-style floor, two solid stainless-steel walls (front and back), and a solid transparent polycarbonate side wall, ceiling, and door. Two pellet dispensers (ENV-203) mounted on the front wall of the operant chambers delivered 45-mg food pellets (Bio-Serv, Flemington, New Jersey, USA) to a food cup (ENV-200R7) on the lower-middle section of the front wall. Head entries into the food magazine were recorded with an infrared photobeam (ENV-254) located near the bottom of the food cup. A house light (ENV-227M) was located on the top-middle of the front wall above the food cup. On either side of the food cup were two retractable levers (ENV-112CM). A cue light (ENV-119M-1) was located above each lever. Water was continuously available through a sipper tube that protruded into the operant chamber from the back wall. The experimental tasks were controlled and recorded with 2-ms resolution by the software program MED-PC IV (Tatham and Zurn, 1989).
Procedure

Initial training

Magazine training consisted of food pellets delivered on a random time 60-s schedule for one session. Next, the rats completed lever training for three sessions, which consisted of food delivery on fixed ratio (FR) 1, random ratio (RR) 3, and RR 5 schedules of reinforcement (see Fig. 1 for a complete timeline). During the RR schedules, both levers were extended, and 3 or 5 responses were required on average to earn one food pellet. For the FR and RR schedules, rats worked on both levers and independent schedules until 20 reinforcers on each lever were earned within a session. Sessions concluded after rats earned 240 pellets or until 2 h elapsed, whichever occurred first.

Impulsive choice task – baseline

The first 12 sessions of the impulsive choice task were designed to test baseline preference for the larger reward/magnitude discrimination in the absence of any delay differences between the levers. Rats chose between the SS and LL levers, both of which delivered food after 5 s. The SS lever resulted in 1 pellet and the LL lever resulted in two pellets. The task consisted of 40 trials, lasting for approximately 1 h, and resulted in a maximum of 66 pellets. Each session contained a random ordering of 12 free-choice trials, 14 SS forced-choice and 14 LL forced-choice trials. On free-choice trials, both levers were inserted into the operant chamber, and the rats chose either lever. After a lever was pressed, the other lever was retracted, and the cue light above the chosen lever was illuminated. The first press after the delay resulted in reward delivery, retraction of the lever, and termination of the cue light. The 60-s inter-trial interval began immediately. Forced-choice trials were identical to free-choice trials, but only one lever was inserted into the operant chamber.

Impulsive choice task – larger-later delay

After the first 12 sessions, the LL delay increased across blocks within each session. The task consisted of 52 trials, lasting approximately 1 h. There were 4 blocks of trials in total with each block consisting of 13 trials. Within each block, there were two LL forced-choice trials, two SS forced-choice trials, and nine free-choice trials. Forced-choice trials were presented in a random order first to inform the rats of the delays associated with each lever. After the forced-choice trials were completed, rats received free-choice trials within the block. In the first block, the SS delay and the LL delay were 5 s, as in the baseline phase of the task. In the subsequent blocks, the LL delay increased to 15, 30, and then 60 s, while the SS delay stayed at 5 s. Rats experienced the impulsive choice task for 25 sessions (Fig. 1).

Drug preparation and administration

Prior to drug administration, rats were trained to drink 0.5 mL of coconut water from a 1-mL syringe in their home cage. The coconut water served as the vehicle for the drug administration phase. Training sessions occurred after each day of initial lever training. Rats continued to experience refresher training with the oral administration procedure once a week to ensure they reliably consumed the coconut water.

Methylphenidate hydrochloride (Sigma-Aldrich, St. Louis, Missouri, USA) was dissolved in coconut water (Vita Coco) to make three stock solutions with concentrations of 2.5, 5.0, and 10.0 mg/mL. Doses were selected based off results showing clinically relevant serum concentration levels of methylphenidate delivered orally to rats in the same manner as described in the current study (Caprioli et al., 2015). The rats’ doses were calculated using the previous day’s weights. Approximately 2 h before administration, the stock solutions were warmed to room temperature. Following initial testing on the impulsive choice task, rats completed each task under four doses of methylphenidate: 0, 2.5, 5, and 10 mg/kg. Each rat experienced each dose for 3 days in a row. The order of doses was determined by a Latin Square. The drug exposure phase lasted 12 days. Rats were dosed individually in an empty cage, which allowed experimenters a clear view to ensure that rats consumed the entire dose. Rats were dosed, placed in the chambers, and a 10-min delay was initiated before the start of the impulsive choice task. The delayed start of behavioral testing after dosing was based off of previous research showing peak plasma concentration of methylphenidate occurred 5 min after dosing and steadily decreased across 60 min after oral administration of methylphenidate to rats (Caprioli et al., 2015). In addition, there were no washout periods delivered during the current study because previous research showed that plasma concentrations of orally-administered methylphenidate were near zero 120 min after oral administration (Caprioli et al., 2015).

Data analysis

Impulsive choice task – larger-later delay

Multi-level repeated-measures logistic regressions were conducted in MATLAB R2020a (The MathWorks;
Natick, Massachusetts, USA) to assess performance in the impulsive choice task. Multi-level modeling assessed differences at the group level (fixed effects) and at the individual level (random effects; Hoffman and Rovine, 2007; Bolker et al., 2008; Young et al., 2013). Fixed effects were entered based on our hypotheses, and these variables were manipulated in the experimental design. Random effects were included to capture unsystematic variance that was not manipulated experimentally. The distribution was specified as a standard binomial and an SS choice was coded as 0 and a LL choice was coded as 1. Individual choice responses were incorporated as correlated observations within individuals to increase the precision of the confidence intervals surrounding the effect size estimates (Cnaan et al., 1997). These qualities of multi-level analyses decrease Type I error rates (provided the models are not over-parametrized; Bates et al., 2015; Matuschek et al., 2017). An α level of 0.05 was used as the reporting threshold for all analyses. Models the effects of the vehicle on impulsive choices are included in Supplemental Materials, Supplemental Digital Content 1, http://links.lww.com/BPHARM/A86.

The first model assessed the last five sessions of the impulsive choice task before drug administration as a measure of baseline differences between the strains. Strain, LL delay, and their interaction were included as fixed effects. The random effects structure was determined by selecting the model with the lowest Akaike’s information criterion (AIC, Akaike, 1974); lower AIC values indicate better fits to the data (Johnson and Omland, 2004). Rat (intercept) and LL delay were tested as random effects. LL delay was significantly correlated with the intercept, indicating over-parameterization (Baayen et al., 2008; Bates et al., 2015), so it was removed from the random effects structure. Strain was entered as a two-level categorical variable. Strain was coded using sum-to-zero coding; Lewis rats were coded as 1 and Wistar rats were coded as −1. The intercept of the model was set at the 5-s LL delay across sessions as well. In addition, an exploratory analysis was conducted to examine whether the rats may have carried over their performance from the end of the previous session to the first block of the next session. Correlations were conducted between the proportion of LL choices at the 60-s LL delay from the previous session and the 5-s LL delay for the next session. A single rater absolute intraclass coefficient was conducted on the proportion of LL choices at the 5-s LL delay across sessions as well.

Exploratory analyses
Two exploratory models were conducted. Model 1 examined strain differences in the first 12 sessions of the baseline impulsive choice task, where the two delays were the same, to assess initial preference for the larger reward and magnitude discrimination. The model included the fixed effects of Strain and Session in a full factorial model with intercept as a random effect. Model 2 included all 25 sessions of the impulsive choice LL delay task prior to drug exposure to assess the session-by-session changes in impulsive choice. Note that the original impulsive choice analyses assessed the last five sessions of the impulsive choice task only. This model included Strain, Session, LL delay, and all interactions as fixed effects. Intercept was entered as a random effect. In both models, the session was treated as a continuous variable. In Model 1, session was centered on the last session to test asymptotic differences and in Model 2, session was centered on the first session to test initial differences.

Results
Impulsive choice task – larger-later delay with methylphenidate
A second multi-level logistic regression was used to measure methylphenidate effects on choice. The model included all 12 days of drug testing on the impulsive choice task. Strain, LL delay, and dose were included as fixed effects in a full factorial model. Rat (intercept), LL delay, and dose were tested as random effects. LL delay was significantly correlated with the intercept, so the final model included rat and dose as random effects. Dose was coded as a continuous variable normalized by dividing by the maximum dose (10 mg/kg). The model tested the 5 mg/kg dose as the intercept based on previous methylphenidate literature where 5 mg/kg resulted in behavioral effects that decreased ADHD-like symptoms (i.e. Bizot et al., 2007). Fifteen individual sessions of data for specific rats were removed because rats did not receive their full doses (approximately 5% of the total data set). These rats did not ingest the full dose during oral administration but did complete the task on these days. Only three rats had more than one session of data removed because of this issue.

**Results**

**Impulsive choice task – larger-later delay with methylphenidate**

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Exploratory analysis below to provide insight into this result.

Lewis and Wistar rats made fewer LL choices as the LL delay increased, \( t = -25.36, P < 0.001, b = -4.26 (-4.59, -3.93) \). Lewis and Wistar rats were not differentially sensitive to LL delay (i.e. their slopes were not significantly different). Supplemental Materials, Supplemental Digital Content 1, http://links.lww.com/BPHARM/A86 depict the impulsive choices across LL delays of the individual rats (see Figure S2, Supplemental Digital Content 1, http://links.lww.com/BPHARM/A86), which are consistent with the group behavior depicted in Fig. 2.

**Impulsive choice task – larger-later delay with methylphenidate**

During methylphenidate exposure, Lewis rats made significantly fewer LL choices than Wistar rats when the delays to both the SS and LL were 5s, \( t = -3.28, P = 0.001, b = -0.93 (-1.48, -0.37) \). This result was consistent with the pre-drug exposure results. Both strains made fewer LL choices as the LL delay increased, \( t = -40.23, P < 0.001, b = -4.68 (-4.91, -4.45) \). The strains did not differ in their sensitivity to delay (slope), but they were differentially sensitive to the doses of methylphenidate, \( t = 2.57, P = 0.010, b = 0.43 [0.10, 0.76] \). As the dose increased, the Lewis rats \( (b = 0.53) \) made more LL choices while the Wistar rats \( (b = -0.33) \) made fewer LL choices (Fig. 3). Overall, the Lewis rats made fewer LL choices and showed a dose-dependent increase in LL choices whereas the Wistar rats showed a dose-dependent decrease in LL choices. However, the Dose × Strain interaction was a relatively small effect. Also, the Lewis rats were still more impulsive than the Wistar rats when tested under methylphenidate (Fig. 3), so methylphenidate did not normalize their choices. Although the methylphenidate effects were small, they were consistent at the individual level (see Supplemental Materials Figure S3, Supplemental Digital Content 1, http://links.lww.com/BPHARM/A86 for graphs of individual rats) which is why the effect was statistically significant.

**Exploratory analyses**

In the impulsive choice task (Fig. 2), Lewis rats chose the LL less often than the Wistar rats when the delay to both rewards was 5s. This observation warranted further investigation because it could indicate poor reward discrimination ability or alterations in reward amount preferences. Alternatively, the Lewis rats may have developed delay aversion to the LL due to the long delays experienced during the choice task. The last delay of each session was 60s, and the rats were strongly SS-preferring during that block of delays. Lewis rats may have carried over the preference from the end of the previous day to the first block of the next session more so than the Wistar rats. We conducted exploratory analyses to address these possibilities. Note that we are considering these models as exploratory because they test predictions that were not a part of our original hypotheses.
Figure 4 shows the 12 sessions of the baseline impulsive choice task where only the magnitude of rewards differed between the SS and LL choices. Lewis rats did not differ from Wistar rats at the end of training. We did not test individual sessions, but there were some sessions where the Lewis rats appeared to have poorer discrimination, even close to the end of training. Consistent with this observation, analysis of the slope indicated that both strains increased LL choices over sessions, $t = 8.73$, $P < 0.001$, $b = 4.97$ (3.85, 6.08), but Lewis rats showed a shallower increase compared to Wistar rats, $t = -2.24$, $P = 0.025$, $b = -1.28$ (−2.39, −0.16) suggesting some impairment in their learning of the LL magnitudes.

When examining the 25 sessions of the impulsive choice task where the LL delay changed within session, Lewis rats made fewer LL choices across all delays in the first session, $t = -2.93$, $P = 0.003$, $b = -0.73$ (−1.22, −0.24) (Fig. 5). Thus, their reduced LL preference was present early in training. Across both strains, the proportion of LL choices decreased across sessions, $t = -3.34$, $P = 0.001$, $b = -0.74$ (−1.18, −0.31), and as LL delay increased, $t = -19.76$, $P < 0.001$, $b = -1.97$ (−2.17, −1.77). This pattern is consistent with the development of delay aversion over sessions. Analyses of the slope of changes over delays and sessions showed that the Session×LL delay, Strain×Session, and Strain×LL delay interactions were significant, but the three-way interaction was not. Analysis of the Session×LL delay interaction showed that LL choices decreased as a function of delay and session, $t = -11.46$, $P < 0.001$, $b = -5.98$ (−7.01, −4.96).

Analysis of the Strain×Session interaction showed Lewis rats’ slope of change across sessions ($b = -1.20$) was steeper compared to Wistar rats ($b = -0.28$), $t = -2.07$, $P = 0.038$, $b = -0.46$ (−0.90, −0.03). In other words, Lewis rats’ overall LL choices decreased more over sessions compared to Wistar rats. Analysis of the Strain×LL delay interaction showed Lewis rats’ slope was shallower compared to Wistar rats, $t = 3.25$, $P = 0.001$, $b = 0.32$ (0.13, 0.52). Wistar rats were more sensitive to delay compared to Lewis rats (see also Fig. 2 for impulsive choice behavior across the last 5 sessions of each delay). Overall, both strains made fewer LL choices as the task progressed, suggesting that both strains were affected by delay aversion due to the experience with longer LL delays, but the Lewis rats were affected to a greater degree.

The patterns in the previous analyses suggest that the longer (i.e. 60-s) LL delay may suppress LL choices over the course of training. To assess this further, the correlation between performance from the last block (60-s LL) of the previous day and the first block of the next day (5-s LL) was assessed. Both strains showed positive correlations (Lewis: $r = 0.30$, $t = 5.31$, $P < 0.001$; Wistar: $r = 0.37$, $t = 6.67$, $P < 0.001$). This suggests that both strains experienced carryover from the end of the previous day to the first block of the next session. To determine whether behavior in the first block was stable over time, we examined the intraclass correlation coefficient (ICC) between 5-s blocks across all 25 sessions of the LL Delay impulsive choice task. Again, both strains showed positive correlations (Lewis: ICC = 0.55, $P < 0.001$; Wistar: ICC = 0.52, $P < 0.001$). Overall, these correlations showed that both strains’ behavior changed over time as they received multiple delays within each session. The 60-s delay may have suppressed responding in a stable manner across sessions.

**Discussion**

The current experiment measured impulsive choices in Lewis rats on and off methylphenidate, a common medication for ADHD, to evaluate this strain as a potential model of ADHD. Consistent with one of our original hypotheses, Lewis rats made more impulsive choices compared to an outbred control strain, the Wistar rat. Oral administration of methylphenidate dose-dependently increased LL choices in Lewis rats, while methylphenidate worsened self-control in Wistar rats. The behavioral patterns found in Lewis rats and their response to methylphenidate were consistent with findings in children and adults with ADHD.

Lewis rats made more impulsive choices at all delays compared to Wistar rats. The Lewis rats’ impulsive behavior in this experiment replicated other experiments when compared to inbred strains (Anderson and Woolverton, 2005; Madden et al., 2008; Anderson and Diller, 2010; Huskinson and Anderson, 2012; Huskinson...
et al., 2012) and Wistars (Garcia and Kirkpatrick, 2013). Overall, these results indicate that the Lewis rat exhibited marked impulsive choices, a key characteristic of ADHD, particularly the hyperactive-impulsive subtype. It is important to note that Lewis rats’ slopes did not significantly differ from Wistar rats’ slopes in the impulsive choice task (Fig. 2), suggesting Lewis rats’ marked impulsive choices may not have been due to increased delay discounting. Delay discounting is the decrease in value of a reward as the delay to the reward gets longer, likely at a hyperbolic rate (Mazur, 2000; Takahashi, 2005; Baumann and Odum, 2012). The current results suggest that increased impulsive choices may have been driven by some other psychological construct such as errors in temporal processing, inability to discriminate between reward size magnitudes, impaired preference for larger magnitudes, or increased delay aversion.

In the current experiment, the Lewis rats’ impulsive choice was still substantial even when the delays to reward were the same for the SS and LL choices, suggesting possible deficits in reward discrimination or preference. Indeed, the Lewis rats did show a shallower slope in their learning curve in the baseline impulsive choice task where the SS and LL were the same delays, but different magnitudes (Fig. 4). While the strains did not differ in the last session of baseline training, there were indications of differences in previous sessions and the strains differed significantly in the first session of impulsive choice testing, prior to experiencing the longer...
delays in that session. The LL choice was more optimal when the delays were the same because it resulted in a larger reward, so both strains should have chosen the LL choice exclusively at the 5-s delay. These results are consistent with a study by Anderson and Woolverton (2005), where Lewis rats completed an impulsive choice task with increasing LL delays. The first delay to reward was 0 s for both choices, but the LL choice resulted in three food pellets while the SS choice resulted in 1 food pellet. Lewis rats chose the LL choice around 80% of the time while the comparison strain chose the LL almost exclusively (Anderson and Woolverton, 2005). Here, with both rewards delayed at 5 s, the Lewis rats showed profound deficits, which may at least partially reflect deficits in magnitude discrimination or preference.

Children with ADHD show similar disruptions in magnitude preference. When children with ADHD were asked to choose between two immediate options ($10 now vs. $10.50, $9.50, and $9.00 now), they made significantly more errors than the matched control group (Wilson et al., 2011). This was proposed to be due to inattention. Lewis rats’ lower LL choices could be due to inattention or poor reward discrimination, either of which might increase random choices. However, an increase in random choices should have resulted in a flatter slope of their choice function which was not the case. It is also possible that the larger magnitude is not valued appropriately in Lewis rats. Further research is needed to further parse apart attention, magnitude discrimination, and larger reward preference deficits in people with ADHD and Lewis rats.

An additional factor was that both strains showed signs of the emergence of delay aversion over the course of the impulsive choice task as rats were exposed to longer delays, and this effect was greater in the Lewis rats. Thus, the results suggest that the Lewis rats experienced more extreme delay aversion than the Wistar rats. The long delays were always delivered on the LL lever, so the LL delay aversion may have caused the Lewis rats to increasingly avoid the LL lever, which may result in reduced LL choices at aversion may have caused the Lewis rats to increasingly avoid the LL lever, which may result in reduced LL choices at delays were always delivered on the LL lever, so the Lewis rats showed profound deficits, which may at least partially reflect deficits in magnitude discrimination or preference.

To our knowledge, this study is the first to test the effects of methylphenidate in Lewis rats. Response to methylphenidate is of key value when considering Lewis rats as a model for ADHD because methylphenidate administration typically decreases behavioral symptoms of ADHD in people. Lewis rats showed modest increases in LL choices as a function of methylphenidate dose (Fig. 3). Interestingly, Wistar rats became more impulsive as a function of methylphenidate dose. The pattern of behavior in the Wistar strain may be related to results reported by Caprioli et al. (2015) where methylphenidate increased impulsive action, measured with the five-choice serial reaction time task. Lister-hooded rats showed heightened levels of impulsivity after methylphenidate exposure. Although preliminary, the current results suggest that individuals that do not have heightened levels of impulsive choices may not benefit from methylphenidate. However, this pattern may be specific to impulsive choice, so future research should evaluate this pattern on other behavioral measures.

There were only modest effects of methylphenidate on impulsive choices in the current experiment, so these results should be interpreted with caution. One reason for the modest effects of methylphenidate may be the route of drug administration. The rats were trained to consume doses of methylphenidate orally to match the most common method of consumption used in humans. However, studies often administer methylphenidate to rodents via intraperitoneal injections. It is possible that this may have affected the results in comparison to other rodent studies due to differences in pharmacodynamics. Moreover, intraperitoneal injections may result in higher peak plasma methylphenidate concentrations compared to oral administration (Patrick et al., 1984). Perhaps more robust results would be obtained with injections of methylphenidate.

Furthermore, analyses of the effects of the vehicle (see Supplemental Materials, Supplemental Digital Content 1, http://links.lww.com/BPHARM/A86) showed that the coconut water produced oppositional effects to methylphenidate on the impulsive choice task. This suggests that the methylphenidate effects may have been underestimated because the vehicle produced effects that may have counteracted methylphenidate. In addition, the differential effects of dose for the strains may be further parsed apart with breaks between doses. We found that Lewis rats made more LL choices as dose increased while Wistar rats made fewer LL choices. Re-establishment of baseline impulsive choice between the dual pathway theory of ADHD suggests that altered motivation in mesolimbic dopaminergic circuitry results in delay aversion (Sonuga-Barke et al., 1992; Sonuga-Barke, 2002), so Lewis rats’ aversion to delays may provide an animal model for studying the neurobiology of delay aversion.
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