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ORIGINAL INVESTIGATION

Pharmacological studies of effort-related decision making using mouse touchscreen procedures: effects of dopamine antagonism do not resemble reinforcer devaluation by removal of food restriction

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Abstract

Rationale Effort-based decision-making tasks offer animals choices between preferred reinforcers that require high effort to obtain vs. low effort/low reward options. The neural mechanisms of effort-based choice are widely studied in rats, and evidence indicates that mesolimbic dopamine (DA) and related neural systems play a key role. Fewer studies of effort-based choice have been performed in mice.

Objectives The present studies used touchscreen operant procedures (Bussey-Saksida boxes) to assess effort-based choice in mice.

Methods CD1 mice were assessed on a concurrent fixed ratio 1 panel pressing/choice procedure. Mice were allowed to choose between rearing to press an elevated panel on the touchscreen for a preferred food (strawberry milkshake) vs. consuming a concurrently available less preferred alternative (high carbohydrate pellets).

Results The DA D_2 antagonist haloperidol (0.05–0.15 mg/kg IP) produced a dose-related decrease in panel pressing. Intake of food pellets was not reduced by haloperidol, and in fact, there was a significant quadratic trend, indicating a tendency for pellet intake to increase at low/moderate doses. In contrast, reinforcer devaluation by removing food restriction substantially decreased both panel pressing and pellet intake. In free-feeding choice tests, mice strongly preferred milkshake vs. pellets. Haloperidol did not affect food intake or preference.

Conclusion Haloperidol reduced the tendency to work for food, but this reduction was not due to decreases in primary food motivation or preference. Mouse touchscreen procedures demonstrate effects of haloperidol that are similar but not identical to those shown in rats. These rodent studies may be relevant for understanding motivational dysfunctions in humans.

Keywords Motivation · Dopamine · Schizophrenia · Bussey-Saksida chambers · Panel pressing · Preference test

Introduction

Loss of motivation, anergia, fatigue, and psychomotor slowing are psychiatric symptoms commonly seen across a broad spectrum of disorders, including depression, schizophrenia, and Parkinson's disease (Salamone et al. 2006, 2016a, 2016b; Treadway et al. 2012; Markou et al. 2013; Culbreth et al. 2018a, 2018b). Considerable research on the neural mechanisms underlying motivational deficits has focused on mesolimbic dopamine (DA) and its related circuits (Salamone and Correa 2012; Mai et al. 2012; Salamone et al. 2016a, b, 2018a, b). Nucleus accumbens DA is a nodal point in the modulation of activational aspects of motivation (i.e., vigor and speed in the instigation and persistence of motivated behavior, work output on instrumental tasks; see review by Salamone et al. 2017). Effort-based decision making has emerged as a commonly used experimental approach for evaluating activational aspects of motivation in animal research. Typically, effort-related choice tasks offer the organism the option of choosing between a preferred reinforcer that requires high effort to obtain (e.g., lever pressing or barrier climbing) vs. concurrently available but less preferred food (Salamone et al. 1991, 1994, 1996, 2009; Pardo et al. 2012; Randall et al.

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2012) or sucrose solution (Pardo et al. 2015; SanMiguel et al. 2018). Several studies involving multiple techniques and different laboratories have demonstrated that interference with DA transmission, either by DA antagonism or depletion, substantially reduces the tendency to exert effort in pursuit of reinforcement (Salamone et al. 1991, 1994; Floresco et al. 2008a; Salamone and Correa 2012; Mai et al. 2012; Nunes et al. 2013; Hosking et al. 2015; Yohn et al. 2015; Salamone et al. 2015, 2016a). Multiple control studies in rats have demonstrated that these effects of DA antagonism, depletion, or altered receptor expression are not due to changes in primary food motivation, food preference, hedonic taste reactivity, discrimination of reinforcement density, reference memory, or delay of reinforcement and do not resemble the effects of pre-feeding, appetite suppressant drugs, or reinforcer devaluation (Salamone et al. 1991, 2002; Sink et al. 2008; Floresco et al. 2008a; Nunes et al. 2013; Pardo et al. 2015; Ward et al. 2012; Randall et al. 2012, 2014; Yohn et al. 2015). Facilitation of DA transmission increases selection of high-effort options (Sommer et al. 2014; Randall et al. 2015; Yohn et al. 2016a, 2016b, 2016c), and considerable evidence indicates that mesolimbic DA is part of a larger forebrain circuitry that regulates exertion of effort and effort-based choice (Mingote et al. 2008; Floresco et al. 2008b; Ghods-Sharifi and Floresco 2010; Bailey et al. 2016; Winstanley and Floresco 2016; Hart et al. 2017, 2018).

While the neural mechanisms underlying effort-related choice performance have been widely studied in rats, fewer studies have been performed in mice. The development of effort-related choice procedures in mice is necessary in order to provide generalizations across species, and also because of the potential value of research using genetically altered mice. Previous mouse studies of effort-based decision making have used a T-maze choice task, in which the mice could choose either to climb a barrier to obtain higher density (HD) of reinforcement or simply approach a lower density (LD) arm without any obstacles (Pardo et al. 2012). Under baseline conditions, mice preferred the HD arm over the LD arm, and this preference was shifted by the DA D_2 antagonist haloperidol (Pardo et al. 2012) and the DA depleting agent tetrabenazine (Correa et al. 2018). Another T-maze task offered mice a choice between running in a running wheel vs. approaching and consuming sucrose pellets; haloperidol decreased time spent running in the wheel and increased intake of sucrose (Correa et al. 2016), and the same effect was observed after tetrabenazine administration (López-Cruz et al. 2018). The results of these T-maze studies in mice indicate that DA D_2 receptors are involved in regulating effort-related decision making and effort expenditure in mice as well as in rats (Pardo et al. 2012; Correa et al. 2016, 2018; López-Cruz et al. 2018).

Effort-related choice procedures involving operant behavior have been used sparingly in mice. Cagniard et al. (2006) showed that knockdown of the DA transporter, which elevates DA transmission, increased selection of high-effort lever pressing and decreased chow intake in mice. This is consistent with Robles and Johnson (2017), who reported that intraventricular injections of the D_2 antagonist eticlopride reduced selection of lever pressing on ratio schedules with high requirements in an effort-based discounting task in mice. In the last few years, mouse touchscreen procedures (e.g., Bussey-Saksida operant boxes) have been developed for the assessment of various cognitive and motivational functions (Markou et al. 2013; Heath et al. 2015; Phillips et al. 2018). Given the importance of this emerging technology and its potential utility for assessing operant behavior in mice, the present paper describes the establishment of mouse touchscreen procedures for the assessment of effort-based choice using a concurrent panel pressing/pellet consumption task that is similar to the concurrent fixed ratio (FR)/chow feeding procedures developed in rats. In addition, the experiments below describe the pharmacological validation of these procedures by assessment of the effects of the DA D_2 antagonist haloperidol. In order to make the physical effort requirement of the panel press more difficult, the instrumental response was altered by raising the target area on the panel above the floor. Animals were given the choice between panel pressing on an FR1 schedule for a preferred liquid milkshake vs. approaching and consuming food pellets that were concurrently available in the chamber. The first experiment assessed the effects of intraperitoneal (IP) administration of haloperidol (0.05–0.15 mg/kg). The second experiment determined the effects of reinforcer devaluation by removal of food restriction, and experiment 3 examined the effects of haloperidol on intake and preference for the same foods used in the touchscreen experiments.

Materials and methods

Animals

Sixteen outbred CD1 male mice (Charles River) were housed individually in a vivarium with a 12-h light/dark cycle (lights on at 07:00). Mice weighed 24–30 g at the beginning of the study (4–5 weeks old), and were food restricted to 85% of their free-feeding body weight for initial operant training, after which modest growth was allowed throughout the experiment. Mice were fed supplemental chow daily to maintain weight, and water was available ad libitum in their home cages. All the behavioral sessions and drug testing were consistently conducted during the light part of the light/dark cycle (1:00–3:00 p.m.) on weekdays, and the same 16 animals were used for all phases of the experiment. All animal protocols were approved by the University of Connecticut Institutional

Animal Care and Use Committee, and followed NIH guidelines.

Pharmacological agents

Haloperidol (Sigma Aldrich Chemical, St Louis, MO), a DA D_2 receptor antagonist, was dissolved in a 0.3% tartaric acid solution (pH = 4.0) to an initial concentration of 1.0 mg/mL and substantially diluted with 0.9% saline to yield target doses (0.05, 0.075, 0.10, and 0.15 mg/kg) that were administered in a volume of 10.0 ml/kg. Because of the substantial saline dilution, saline served as the vehicle control for haloperidol. Dose selection was based on pilot studies as well as previously published studies (Correa et al. 2016). All injections were administered intraperitoneally, and the lead time was 50 min. The injection volume for each mouse was 0.1 mL/10 g.

Apparatus and materials

Behavioral sessions were conducted in Bussey-Saksida touchscreen chambers (Campden Instruments Led, Loughborough, UK), each consisting of a touchscreen (30.7 cm, resolution 800 × 600), an operant arena, and a feeder. The operant arena was enclosed by trapezoidal walls and touchscreen, situated directly across from the feeder. The reinforcer for panel pressing was strawberry nutrition shake (Ensure Plus, Abbott Nutrition, Columbus, OH), which was delivered to the feeder magazine by the liquid diet dispenser. Food preference tests were conducted in empty home cages, and modified pipette tips (5.0 mL, Gilson) were used to deliver the milkshake, which the mice could obtain by licking the nozzle.

Reinforcer exposure and initial training

Before the operant training, each mouse was exposed to 1-mL strawberry shake in home cage for 2 days in order to become familiar with the reinforcer. Mice were then introduced to a 30-min initial magazine training session for 3 days, during which the feeder delivered 20 μL of the reinforcer automatically every 30 s, or 60 μL if a response to the visual stimulus/touch panel was made (reset the 30-s count). The stimulus was presented on the touchscreen as a white square panel (4.57 × 4.57 cm) on a black background located towards the bottom of the screen (1.52 cm from the floor). Completing a panel press disabled the panel, illuminating the magazine, and delivering the reinforcer along with a tone (1000 ms, 3 kHz). This stimulus combination signaled reinforcer delivery throughout the experiment. The mouse must nose-poke to break the infrared beam in the feeder in order to reactivate the panel on the screen for future responding. In order to prepare mice for the choice food pellet exposure, a dish of 15 pellets was introduced in the home cages daily for 2 days before the FR1/choice task commenced.

Development of the concurrent FR/choice task

Followed by the initial magazine training, mice were trained to press on a continuous reinforcement (i.e., FR 1) schedule in 30-min sessions, 5 days a week. After the mice reached a stable response pattern (2 weeks with at least 30 panel presses per day), the panel was raised to the center of the touchscreen (6.1 cm from the floor) so that the mice had to rear up to press it. This change was important because it increased the physical effort requirement involved in panel press. After 4 weeks of training on FR1 with raised panel, all mice met the criterion of > 200 panel presses per day, so the mice were shifted to the concurrent FR/choice task. In this task, a dish of weighed high carbohydrate pellets (45 mg, Bio-Serv, Frenchtown, NJ) was used as a concurrent choice food and was placed in each chamber. The dish of pellets was placed between touchscreen and magazine against the left side of the chamber. Pellet intake was determined by weighing the remaining pellets including spillage after each session. The timeline for the initial training, and all drug experiments, is shown in Fig. 1.

Experiment 1: Effects of haloperidol on concurrent FR1/choice task

Mice were trained on FR1/choice task up to 4 weeks, and they received one habituation injection (0.1 mL saline) 1 week before the drug testing phase. On drug test days, all mice received vehicle and following doses of haloperidol: 0.05, 0.1, and 0.15 mg/kg, in a randomly varied order. This experiment used a within-groups design. Mice received one drug treatment per week, and there was a 4-day baseline training before the next drug test day. All injections were given 50 min before testing started.

In addition to the aforementioned doses, an additional experiment conducted a probe test to determine if 0.075 mg/kg haloperidol, which is intermediate between the two highest doses used previously, could decrease lever pressing and increase pellet intake. Two weeks after the completion of previous drug treatments, all mice received vehicle or 0.075 mg/kg haloperidol in a randomly varied order, one treatment per week.

Experiment 2: Effects of pre-feeding on concurrent FR1/choice task

Following one additional training week on FR1/choice task, all mice were taken off food-restriction and were pre-fed 24 h prior to the testing session. Baseline was acquired from the last day of the training days. Panel pressing and pellet intake were

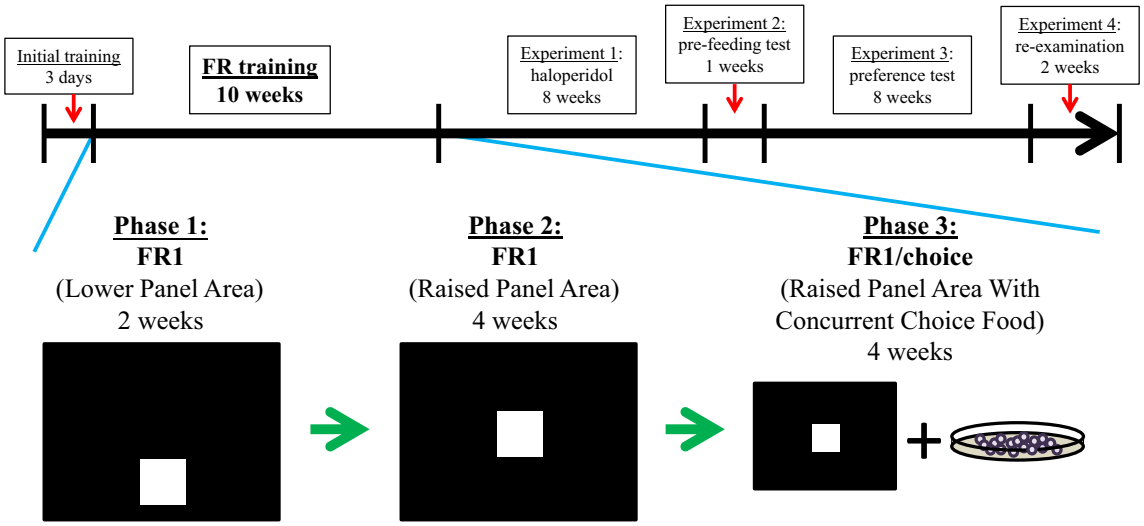

Fig. 1 Timeline showing the successive phases of training and drug testing during each experiment

measured on the pre-fed day and were compared to baseline day while animals were food-restricted.

Experiment 3: Effects of haloperidol on reinforcer intake and preference

Food preference test was conducted in empty home cages to determine the preference between milkshake and pellet used in effort-related task. Each mouse was put back on food restriction, and was first trained for 2 weeks to access the milkshake by licking the nozzle of a modified pipette tip. And then they were exposed to a dish of pellets for another week. Subsequently, each mouse was allowed to approach and consume either milkshake or pellets freely in 30-min sessions for 2 weeks. On drug testing days, all mice received vehicle and following doses of haloperidol: 0.05, 0.1, and 0.15 mg/kg, in a randomly varied order.

Experiment 4: Re-examination of the effects of haloperidol on FR1/choice task

After the completion of the food restriction and preference tests, haloperidol challenge was conducted again in order to determine if haloperidol was still having effects on panel pressing after all the other experiments were finished, especially in consideration of the lack of effect of haloperidol on food intake and preference in experiment 3. Mice were retrained on FR1/choice task for 1 week, and received vehicle and highest dose of haloperidol (0.15 mg/kg) in a randomly varied order.

Statistical analyses

The main dependent variables of interest were total number of panel presses and gram quantity of pellet intake during 30-min sessions. Data were analyzed with repeated measures of analysis of variance (ANOVA) designs using a statistical program (SPSS 23.0 for Windows). To determine the differences between treatment conditions, non-orthogonal planned comparisons were used if the overall ANOVA was significant, following procedures described in Keppel (1991). Overall error term was used, and the number of comparisons was restricted to the number of treatments minus 1. Additionally, *t* tests were used to determine the treatment difference for experiments in which two conditions were assessed (e.g., experiment 2 and 4). All data were presented as mean ± SEM, and significance level was set at $\alpha = 0.05$. All figures were created by the use of SigmaPlot 10.0.

Results

Experiment 1: Effects of haloperidol on concurrent FR1/choice task

Figure 2 shows the effects of systemic administration of haloperidol on FR1/choice task. Repeated measures ANOVA revealed that haloperidol had a significant suppression effect on panel presses (Fig. 2a, $F(3, 45) = 20.489$, $p < 0.001$). Planned comparisons revealed that 0.1 and 0.15 mg/kg haloperidol significantly reduced lever pressing compared to vehicle treatment (0.1 mg/kg, $p < 0.01$; and 0.15 mg/kg, $p < 0.001$). However, haloperidol had no overall effect on pellet intake (Fig. 2b, $F(3, 45) = 1.747$, n.s.). In fact, an orthogonal analysis of trend revealed a significant quadratic trend ($p < 0.05$) for the effect on pellet intake, demonstrating a trend towards an increase at moderate doses. For the haloperidol probe dose (0.075 mg/kg) test, paired-sample *t* test revealed that the haloperidol had significant suppression effect on panel press compared to vehicle treatment (Fig. 3a, $t(15) = 3.201$,

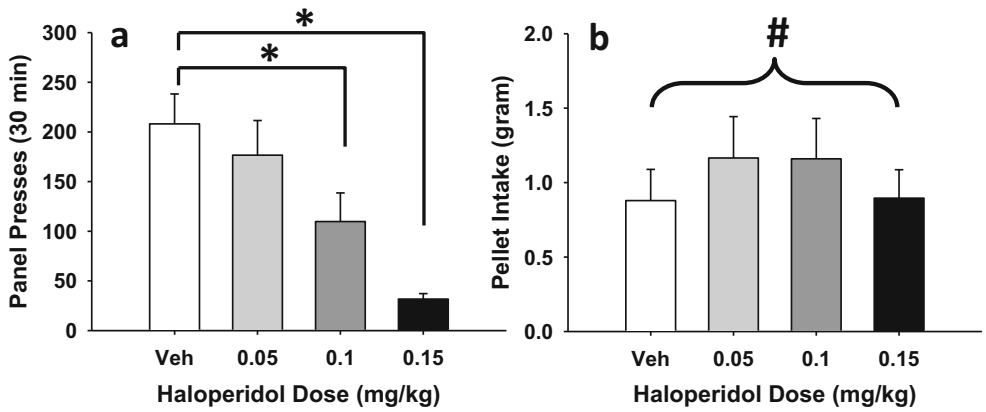

Fig. 2 Effects of haloperidol on touchscreen choice performance in mice. **a** Mean (+ SEM) number of panel presses after treatment with vehicle and various doses of haloperidol ($n = 16$). *$p < 0.05$, different from vehicle, planned comparison. **b** Mean (+ SEM) intake of food pellets (in grams) after treatment with vehicle and various doses of haloperidol. There was a significant quadratic trend indicates a trend towards an increase choice food intake at moderate doses (#$p < 0.05$, orthogonal analysis of trend)

$p < 0.01$), and there was a trend towards an increase in pellet intake ($p = 0.067$, Fig. 3b).

Experiment 2: Effects of pre-feeding on concurrent FR1/choice task

Figure 4 shows the effects of 24-h pre-feeding on FR1/choice task. The paired-sample t test indicated that the effects of pre-feeding significantly suppressed both panel pressing (Fig. 4a, $t(15) = 5.852$, $p < 0.001$), and pellet intake (Fig. 4b, $t(15) = 4.119$, $p < 0.01$).

Experiment 3: Effects of haloperidol on reinforcer intake and preference

Systemic administration of haloperidol had no effect on the preference between liquid diet milkshake and high carbohydrate pellet. Both types of food consumption were recalculated as kilo-calories for comparison purposes, so that they could be represented on the same scale. Factorial ANOVA indicated a significant difference for consumption of the two foods, with mice strongly preferring the milkshake over the pellets (Fig. 5, $F(1, 15) = 37.488$, $p < 0.001$). However, there was no significant effect of haloperidol treatment ($p = 0.820$), and no treatment x food type interaction ($p = 0.595$), demonstrating that haloperidol had no effects on intake or preference of the two food sources in free-feeding tests.

Experiment 4: Re-examination of the effects of haloperidol on FR1/choice task

Figure 6 shows the effects of 0.15 mg/kg haloperidol on FR1/choice task. Paired-sample t test indicated that the haloperidol significantly suppressed panel presses (Fig. 6a, $t(15) = 9.244$, $p < 0.001$) but no effect on pellet intake (Fig. 6b, $p = 0.456$). These results demonstrate that mice were still sensitive to the effects of haloperidol at the end of entire series of experiments.

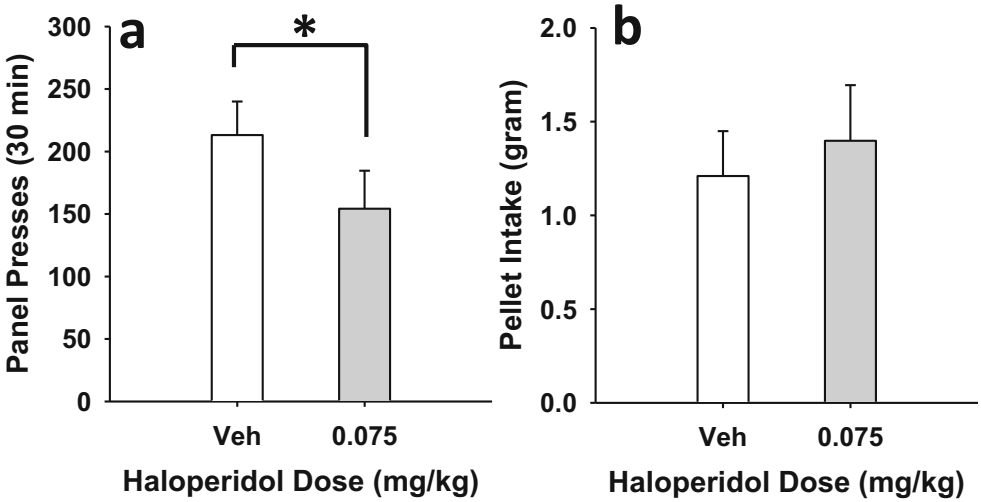

Fig. 3 Effects of 0.075 mg/kg haloperidol on touchscreen choice performance in mice. **a** Mean (+ SEM) number of panel presses after treatment with vehicle and 0.075 mg/kg haloperidol ($n = 16$). *$p < 0.05$, different from vehicle, planned comparison. **b** Mean (+ SEM) intake of food pellets (in grams) after treatment with vehicle and 0.075 mg/kg haloperidol. There was a tendency towards an increase in pellet intake at this dose ($p = 0.067$)

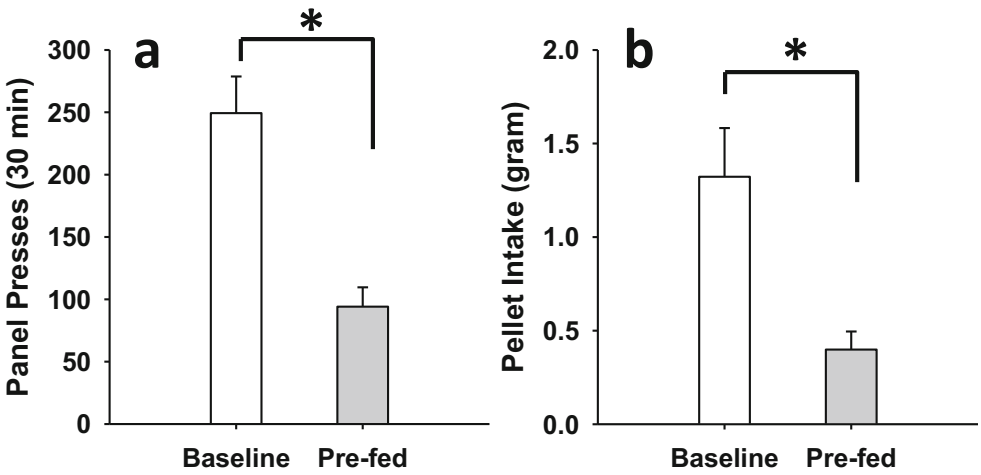

Fig. 4 Effects of reinforcer devaluation by prefeeding on touchscreen choice performance in mice. **a** Mean (+ SEM) number of panel presses after baseline and prefeeding days. **b** Mean (+ SEM) intake of food pellets (in grams) after baseline and prefeeding days. Unlike haloperidol, prefeeding decreased both panel pressing and pellet intake ($n = 16$). *$p < 0.05$, different from baseline

Moreover, the similar results of administration of 0.15 mg/kg haloperidol in experiments 1 and 5 (Figs. 2a and 6a) indicate that despite the repeated exposures to haloperidol across the experiments, there was no sensitization effect that enhanced the effects of 0.15 mg/kg.

Discussion

Rodent studies of effort-based choice are significant because they shed light on a fundamental aspect of motivation, and also because of their potential clinical relevance. Human studies of effort-based decision making have reported that several pathological conditions, including major depression, Parkinson's disease, and schizophrenia, are characterized by a reduced willingness to expend effort to obtain rewards (Treadway et al. 2012; Gold et al. 2013; Chong et al. 2015; Salamone et al. 2016a, 2016b; Culbreth et al. 2018a, 2018b). Although most of the rodent work employing operant

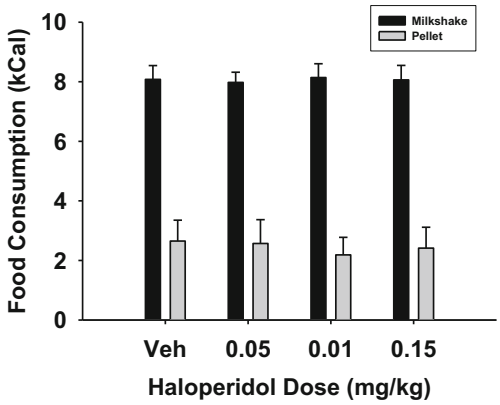

Fig. 5 Effects of haloperidol on intake of strawberry Ensure milkshake and food pellets in the free feeding preference tests. Mean (+ SEM) intake (in kCal) for both types of foods is shown. There were no significant effects of haloperidol on intake of either food, and the lack of significant interaction indicates a lack of change in preference ($n = 16$)

behavior methods in this area has focused on rat studies, the present experiments demonstrated the successful validation and optimization of an effort-related choice task using Bussey-Saksida touchscreen apparatus in mice. Under baseline conditions, CD1 mice showed highly motivated panel pressing behavior and ate little of the concurrently available food in FR1/choice task. Furthermore, the DA D_2 antagonist haloperidol produced a suppressive effect on panel pressing but did not decrease food pellet intake. In fact, orthogonal analysis of trend indicated that there was a tendency for pellet intake to increase at moderate doses of haloperidol, as marked by the significant quadratic trend. To our knowledge, the present study is the first to examine the effects of DA antagonism on effort-related choice using touchscreen chambers in mice. The suppressive effect of haloperidol on panel pressing was not due to changes in food preference or consumption, as indicated by free feeding preference tests. In contrast, reinforcer devaluation by removal of food restriction significantly reduced both panel presses and choice food intake, which is very different from the effects of haloperidol. Taken together, this work suggests that the effort-related choice paradigm conducted in touchscreen chambers may be a useful tool for investigating effort-related motivational functions in mice.

Effort-related decision-making tasks have been widely studied in rats (Salamone and Correa 2012; Salamone et al. 2016b, 2017, 2018a, 2018b); however, fewer studies of effort-based choice have been performed in mice. This could be due to several advantages of using rats, such as ease in handling and better spatial resolution with regard to surgical manipulations in the central nervous system. Although rat-based studies in neuroscience have outnumbered those that have employed mice for decades, there is a shift in the rodent research, such that mouse studies are rapidly overtaking rat studies in recent years (Ellenbroek and Youn 2016). Consistent with this trend, an increasing number of studies using mice in motivation research highlights the importance of studying mice. Procedures that have been used to assess the effort-related

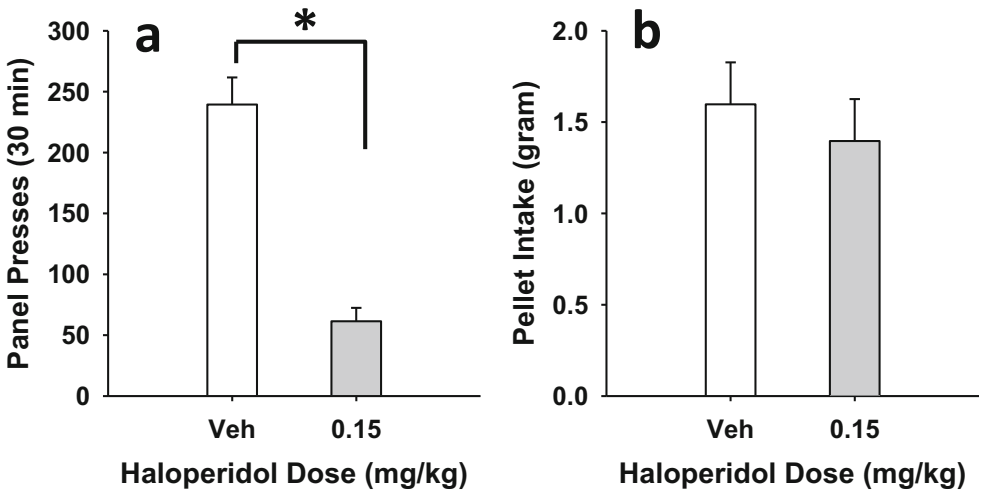

Fig. 6 Effects of 0.15 mg/kg haloperidol on touchscreen choice performance in mice. **a** Mean (+ SEM) number of panel presses after treatment with vehicle and 0.15 mg/kg haloperidol ($n = 16$). *$p < 0.05$, different from vehicle, planned comparison. **b** Mean (+ SEM) intake of food pellets (in grams) after treatment with vehicle and 0.15 mg/kg haloperidol

choice behavior in mice have involved T-maze barrier choice (Pardo et al. 2012; Correa et al. 2016, 2018; López-Cruz et al. 2018) and lever pressing choice tasks (Cagniard et al. 2006; Trifilieff et al. 2013; Robles and Johnson 2017). Heath et al. (2015) provided an initial report on the use of Bussey-Saksida touchscreen chambers in mice for the behavioral assessment of effort expenditure and effort-based choice. They found that the DA D2 antagonists sulpiride and raclopride decreased panel presses in mice tested on a conventional progressive ratio schedule that did not involve the option of an alternative food source. Furthermore, they trained mice ratio schedules (FR16, 32, and 40) with lab chow concurrently available in the chamber, and reported that increasing the ratio requirement caused animal to consume more chow (Heath et al. 2015).

The present studies used an FR1 schedule, and the physical effort requirement was increased by raising the target panel (i.e., a white square) off the floor of the cage instead of on the bottom. These changes in the touchscreen procedure minimized the impact of brief or incidental contact (e.g., tail contact, or brushing with the flank) with the panel as a factor. The results showed considerable similarities between the mice in our touchscreen procedure and rats in lever pressing choice procedures. Specifically, CD1 mice showed persistent panel pressing with relatively low consumption of concurrently available food, which is comparable to rats tested on FR/choice tasks (Salamone et al. 1991, 1996, 2002; Nunes et al. 2013; Yohn et al. 2015; Pardo et al. 2015). As a result, the present studies showed that CD1 mice could maintain vigorous and repetitive panel pressing for a preferred liquid diet in the presence of an alternative food source, which demonstrates a successful adaptation of FR/choice task using the touchscreen system in mice.

The results of experiment 1, in which the effects of the DA D_2 antagonist haloperidol were evaluated, indicated that haloperidol produced a dose-dependent suppression of panel presses. Although there was a clear reduction in panel presses in the current study, haloperidol did not decrease intake of the concurrently available food pellets, suggesting that primary food motivation remained intact after drug injection. In fact, there was a significant quadratic trend (see Keppel 1991 for a discussion of trend analysis), which demonstrates the tendency for pellet intake to increase at low/moderate doses (Fig. 2b). Moreover, results of the second experiment, which probed the effect of 0.075 mg/kg haloperidol, showed not only a suppression of panel presses, but also a strong tendency to increase pellet intake ($p = 0.067$, Fig. 3b). Nonetheless, unlike previous studies using rats in FR/choice tasks, haloperidol-treated mice did not massively increase intake of the alternative food present in the chamber. In many previous studies, rats tested on tasks that offer a choice between lever pressing and chow intake have shown three- to fivefold increases in chow intake after treatment with DA antagonists (Salamone et al. 1991, 2002; Sink et al. 2008). This could reflect rat vs. mouse species differences in the magnitude of food consumption over short periods of time. Despite many common similarities shared among rodent species, some cognitive and behavioral differences have been reported by studies that compared animals between, as well as within, individual rodent strains (Ellenbroek and Youn 2016).

Although a possible explanation for this pattern of results could be that mice treated with haloperidol showed some kind of primary motivation or general "reward" deficit that resulted in less preference for the liquid reinforcer, this assumption can be ruled out because haloperidol-treated mice did not show reduced milkshake intake during the free-feeding preference tests, and still strongly preferred the milkshake over pellets in that experiment (Fig. 5). Furthermore, it is important to note that the pattern of effects induced by haloperidol in these experiments was not mimicked by reinforcer devaluation that was induced by removal of food restriction. Food restriction is widely reported to enhance the reinforcing value of food in

humans and other animals (e.g., Hogenkamp et al. 2017). The results of experiment 3 demonstrated that removal of food restriction to blunt primary food motivation and reduce the value of food reinforcement substantially reduced food pellet intake as well as panel pressing, which is very different from the pattern of effects induced by haloperidol. These findings are consistent with rat studies showing that reinforcer devaluation or administration of appetite suppressant drugs produces effects on effort-based choice that are different than those induced by DA antagonists or accumbens DA depletions (Salamone et al. 1991, 2002; Sink et al. 2008; Randall et al. 2012, 2014). Taken together, these data indicate that haloperidol-induced suppression of panel presses in the present study was not due to changes in food intake, preference, or primary food motivation. This finding is highly relevant because there is an extensive behavioral literature demonstrating that primary food motivation underlies the primary or unconditioned reinforcing properties of food (Salamone and Correa 2002, 2009).

A more complicated question is whether or not a disruption of some aspect of motor function contributed to the suppression of panel pressing. The dose range used for haloperidol was relatively low (0.05, 0.1, and 0.15 mg/kg) compared to doses that are used to induce catalepsy. For example, Santillan-Urquiza et al. (Santillán-Urquiza et al. 2018) administered doses of 0.25, 0.5, and 1.0 mg/kg to mice, and found that only 1.0 mg/kg induced catalepsy. In fact, 1.0 mg/kg is a commonly used dose for induction of catalepsy in mice (e.g., Sharma et al. 2018). Furthermore, none of the doses of haloperidol used was high enough to suppress drinking of the liquid diet or eating the hard food pellets, which are motoric responses that involve postural control as well as head, orofacial, and forelimb motor functions. However, several questions remain. The focus of the present work was on physical effort as opposed to cognitive effort (see Hosking et al. 2015), and thus the present procedures of necessity involve aspects of motor function. So, it is possible that subtle motor dysfunctions contributed to the haloperidol-induced suppression of panel pressing (e.g., Robles and Johnson 2017). In the present studies, we did not assess behavioral measures such as magazine latencies and post-reinforcement pauses or horizonal motor activity, which would be useful measures to obtain in future research. Previous studies have shown that 0.1 mg/kg haloperidol could suppress rearing in CD1 mice exposed to a novel environment (Pardo et al. 2013). Nevertheless, novelty-induced locomotion and rearing, as well as magazine latencies and pauses, are not simply motor responses, because they also involve responsiveness to motivational conditions. In fact, it is clear from the behavioral science literature that there is considerable overlap between aspects of motor and motivational function (Salamone et al. 2017), and behavioral activation, response vigor, and effort-related processes mediated by DA are clearly at the cusp of these two constructs (Salamone and Correa 2002, 2012, Salamone et al. 2018a, 2018b). This overlap between motor and motivational function is also present clinically, as depressed people show psychomotor slowing and reductions in locomotion (Todder et al. 2009). Further research will be needed to characterize the precise mechanisms underlying the suppression of touchscreen panel pressing induced by DA D_2 receptor antagonism.

An important application of the present studies is that this optimized touchscreen paradigm in mice provides a framework for future research involving genetic mouse models. Transgenic and knock-out mouse models have been used to unravel the important role of DA and adenosine in effort-related decision making. For example, in T-maze choice tasks, mice with adenosine A_{2A} receptor knock-out were resistant to the haloperidol-induced changes in selection of the arm with the barrier (Pardo et al. 2012; Correa et al. 2016). Moreover, in studies involving lever pressing choice procedures, mice with DA transporter knockdown or overexpression of nucleus accumbens D_2 receptors induced in adulthood showed increased lever pressing compared to wild-type mice (Cagniard et al. 2006; Trifilieff et al. 2013). In contrast, several studies have shown that D_2 receptor overexpression present from birth leads to decreased selection of FR lever pressing in mice tested on effort-based choice procedures, an effect that may be related to negative symptoms of schizophrenia (Ward et al. 2012; Bailey et al. 2016; Filla et al. 2018). The present work has significance in terms of establishing a touchscreen methodology that allows future studies to examine the underlying functions of important genes in this critical field. Current research in our laboratory is focusing on the role of different polymorphisms of the catechol-O-methyltransferase gene (e.g., Risbrough et al. 2014) on effort-based choice (Yang et al. 2018).

In conclusion, the present studies demonstrate that mouse touchscreen procedures can be used to assess the effects of drugs on effort-based choice in mice. CD1 mice showed highly motivated and persistent panel pressing behavior which is highly comparable to that shown by rats in lever pressing choice procedures. The haloperidol-induced suppression of panel pressing was not due to alterations in food preference, appetite, or reinforcer consumption and did not resemble the effects of reinforcer devaluation by pre-feeding. These results are similar to, but not identical to, previous results with rats. Although rodents share many behavioral and cognitive similarities between species, it is a truism that mice are not simply smaller rats. Considering the importance of cross-species validation and translational research, the present studies established a paradigm that could be useful for future studies using transgenic and knock-out mice models. Moreover, although haloperidol is frequently used as a DA antagonist in behavioral studies, it is possible that this drug is having other neurochemical effects at the doses used. Future research should employ a wider range of DA antagonists with distinct

patterns of affinity and selectivity for different DA receptors. Ultimately, this work could contribute to preclinical research and facilitate the development and testing of therapeutic treatments for motivational deficits seen in patients with schizophrenia, depression, and other disorders.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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