Original Paper

Blockade of dopamine D_1-family receptors attenuates the mania-like hyperactive, risk-preferring, and high motivation behavioral profile of mice with low dopamine transporter levels

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Morgane Milienne-Petiot[1,2], Lucianne Groenink[2], Arpi Minassian[1] and Jared W Young[1,3]

Abstract

Background: Patients with bipolar disorder mania exhibit poor cognition, impulsivity, risk-taking, and goal-directed activity that negatively impact their quality of life. To date, existing treatments for bipolar disorder do not adequately remediate cognitive dysfunction. Reducing dopamine transporter expression recreates many bipolar disorder mania-relevant behaviors (i.e. hyperactivity and risk-taking). The current study investigated whether dopamine D_1-family receptor blockade would attenuate the risk-taking, hypermotivation, and hyperactivity of dopamine transporter knockdown mice.

Methods: Dopamine transporter knockdown and wild-type littermate mice were tested in mouse versions of the Iowa Gambling Task (risk-taking), Progressive Ratio Breakpoint Test (effortful motivation), and Behavioral Pattern Monitor (activity). Prior to testing, the mice were treated with the dopamine D_1-family receptor antagonist SCH 23390 hydrochloride (0.03, 0.1, or 0.3 mg/kg), or vehicle.

Results: Dopamine transporter knockdown mice exhibited hyperactivity and hyperexploration, hypermotivation, and risk-taking preference compared with wild-type littermates. SCH 23390 hydrochloride treatment decreased premature responding in dopamine transporter knockdown mice and attenuated their hypermotivation. SCH 23390 hydrochloride flattened the safe/risk preference, while reducing activity and exploratory levels of both genotypes similarly.

Conclusions: Dopamine transporter knockdown mice exhibited mania-relevant behavior compared to wild-type mice. Systemic dopamine D_1-family receptor antagonism attenuated these behaviors in dopamine transporter knockdown, but not all effects were specific to only the knockdown mice. The normalization of behavior via blockade of dopamine D_1-family receptors supports the hypothesis that D_1 and/or D_5 receptors could contribute to the mania-relevant behaviors of dopamine transporter knockdown mice.

Keywords

Iowa Gambling Task, risk-taking, D_1-family receptors, cognition, bipolar disorder, mania, dopamine transporter knockdown, breakpoint, locomotor activity, Behavioral Pattern Monitor

Introduction

Bipolar disorder (BD) is a serious and debilitating disease with a high prevalence (approximately 2.6% of the population; Merikangas et al., 2011). BD is characterized by manic and depressive mood states and is otherwise known as manic-depressive illness. Mania is the defining feature of BD however, and understanding the mechanisms underlying this state is required for targeted treatments to be developed. Symptoms of mania include hyperactivity, elevated hedonia, risk-preference, and increased motivation or proclivity to engage in goal-directed activity (American Psychiatric Association, 2013). Between each extreme state, people with BD experience euthymia, a state in which they are able to function almost normally, although some symptoms persist including higher novelty exploration (Minassian et al., 2011), and risk-preference during learning (Adida et al., 2011; Henry et al., 2013; van Enkhuizen et al., 2014). These neurocognitive and behavioral impairments correlate with problems in everyday functioning (Green, 2006), leading to the premise that if their cognition could be improved, these patients may be able to better function in society. To date however, approved treatments for BD do not adequately or remediate these behavioral impairments.

A major target for improving functioning in patients with BD is to improve impulse control and remediate high reward-preferences

[1]Department of Psychiatry, University of California San Diego, La Jolla, USA
[2]Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
[3]Research Service, VA San Diego Healthcare System, San Diego, USA

Corresponding author:
Jared W Young, Department of Psychiatry, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0804, USA.
Email: jaredyoung@ucsd.edu

leading to risk-taking behaviors (Adida et al., 2011; Ibanez et al., 2012; Jollant et al., 2007; van Enkhuizen et al., 2014). This preference can be quantified in laboratory settings using the Iowa Gambling Task (IGT; Bechara et al., 1994). The IGT is a complex yet real-world decision-making task requiring learning, motivation, working memory, and problem solving. Hence, a treatment that can reduce the risk-preference of patients with BD in the IGT may prove to be a valuable therapeutic in patients. The IGT can also be examined in rats (Rivalan et al., 2009), and mice (Milienne-Petiot et al., 2017; van Enkhuizen et al., 2014) making this a valuable cross-species task. Additionally, patients with BD exhibit increased motivation during periods of mania (Cassidy et al., 1998). One way to operationalize motivation is via the Progressive Ratio Breakpoint (PRB) test, which originated from pre-clinical studies in animals but is increasingly being used in human studies (Wolf et al., 2014). It measures the maximum effort an individual is willing to exert for a reward while the effort required increases progressively. Few studies have been conducted using this task in humans, although one study observed that patients with unipolar or BD depression exhibited lower motivation as measured by a lower breakpoint compared to healthy controls (Hershenberg et al., 2016), as did patients with schizophrenia (Wolf et al., 2014). While also used in addiction studies (Audrain-McGovern et al., 2014), to our knowledge no PRB studies have quantified motivation in patients with BD mania. Finally, levels of activity and exploration can be quantified across species using the Behavioral Pattern Monitor (BPM), with evidence of a unique hyperactive profile in patients with BD mania (Minassian et al., 2011; Perry et al., 2009). Hence, several cross-species tasks exist in which the mechanisms underlying risk-preference, hypermotivation, and hyperexploration can be examined with relevance to BD.

To model BD mania-relevant behaviors, we have repeatedly demonstrated that reducing dopamine transporter (DAT) function (the primary mechanism underlying neuronal dopamine clearance), recreates many of those behaviors. Reduction of DAT function can be achieved by pharmacological manipulations using the selective DAT inhibitor GBR12909 or by using genetic DAT knockdown (KD) mice compared to their wild-type (WT) littermates. Using these models, a BD mania-like hyperexploratory profile as measured in the BPM was observed (Milienne-Petiot et al., 2017; Perry et al., 2009), together with increased motivation to work for food reward as measured in the PRB test (Cagniard et al., 2006a; Milienne-Petiot et al., 2016), and higher risk-preference in the IGT (Milienne-Petiot et al., 2017; van Enkhuizen et al., 2014). Furthermore, we have demonstrated the pharmacological predictive validity of this model given that chronic administration of the drugs used for the treatment of BD mania, valproate and lithium, attenuate the hyperactivity of KD mice in the BPM without affecting their WT littermates (Milienne-Petiot et al., 2016; Ralph-Williams et al., 2003; van Enkhuizen et al., 2014). Consistent with the experience of some mania patients, however, these treatments were only partially effective as they did not attenuate all mania-relevant behaviors. Identifying the mechanism(s) driving these deficits in mice may aid in identifying novel therapeutics for the treatment of BD mania.

DAT KD mice express only 10% of DAT levels and thus exhibit chronically elevated levels of extracellular striatal dopamine (Zhuang et al., 2001), likely increasing the activation of post-synaptic dopamine receptors, e.g. dopamine D_1 receptors. Zhuang and colleagues reported that there was no change in postsynaptic dopamine D_1 or D_2 receptor levels, although a 50% reduction in D_2 autoreceptor levels were observed in DAT KD mice vs their WT littermates. Evidence of normal autoreceptor-mediated inhibition of dopamine release between these two genotypes however, lead to the hypothesis that autoreceptor function remained unchanged in DAT KD mice. Hence, other mechanisms require investigation.

Dopamine receptor agonists have been associated with increased motivation and risky decision-making (Burdick et al., 2014). Thus, the elevated activation of dopamine D_1 receptors in DAT KD mice could mediate their mania-relevant profile. In fact, blockade of the dopamine D_1 receptors reduced impulsivity and reward-seeking behavior in rats and mice (Beninger and Miller, 1998), while suppression of striatal dopamine D_1 receptors impaired reward-associative learning (Higa et al., 2017). SCH 23390 hydrochloride (SCH)-treatment to rats reduced sucrose seeking (Grimm et al., 2011), and given that SCH is an enantioselective dopamine D_1 receptor (Ki=0.2 nM) and dopamine D_5 receptor (Ki=0.3 nM) antagonist, the important effect of the dopamine D_1-family receptors on reward-related behaviors supports our hypothesis of its involvement in mania-relevant behaviors of DAT KD mice. We therefore assessed whether SCH treatment would selectively attenuate BD mania-relevant behavior of DAT KD mice at doses that would not affect their WT littermates.

Methods

Animals

Fifty-six male DAT KD (n=25) mice and their WT (n=31) littermates aged nine months and weighing approximately 25 g were used in this study. These mice were previously tested in the same tasks and had been treated with a serotonin-dopamine modulator (brexpiprazole; Milienne-Petiot et al., 2017) after receiving a three-week washout period. The mice received this previous treatment in a within-subject design, hence all mice were treated with the same doses of this modulator. The mice were generated from DAT heterozygous breeders backcrossed onto a C57BL/6J background for more than 10 generations, originally sent from the University of Chicago (Zhuang et al., 2001). Mice were group housed (maximum four/cage) and maintained in a temperature-controlled vivarium (21±1°C) on a reversed day-night cycle (lights on at 19:00, off at 07:00). All mice had ad libitum access to water and were food-restricted to 85% of free-feeding body weight during periods of testing. Procedures were approved by the UCSD Institutional Animal Care and Use Committee. The UCSD animal facility meets all federal and state requirements for animal care.

Drug treatment

SCH was purchased from Tocris Bioscience (Bristol, UK). The required amounts of SCH were dissolved in 0.9% saline vehicle. For the IGT and BPM study, mice were administered SCH at 0.01 and 0.03 mg/kg or vehicle by intraperitoneal (i.p.) injection 10 min prior to testing at a volume of 5 mL/kg. Doses were determined based on previous studies performed in rats (Grimm et al., 2011), after extrapolation (Nair and Jacob, 2016; Sharma and

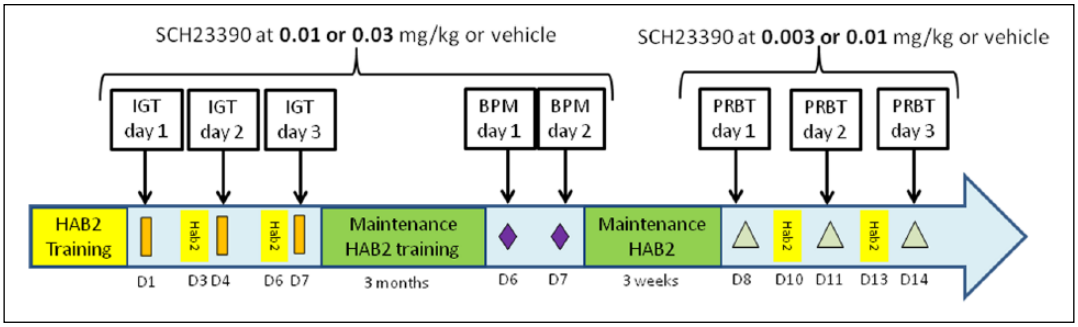

Figure 1. Testing schedule. Timeline of the different experiments using dopamine transporter (DAT) knockdown (KD) and wild-type (WT) mice treated with SCH 23390 hydrochloride (SCH) at different doses or vehicle. Mice (n=56) were tested in the Iowa Gambling Task (IGT) on three different days in a within-subject study design. After a wash-out period the same group of mice was tested in the Behavioral Pattern Monitor (BPM) on two subsequent days in the between-subject study design. Finally, the mice were tested in the Progressive Ratio Breakpoint (PRB) test on three different days in the within-subject study design. For the IGT and PRB testing periods, mice were trained on phase 2 (Hab2) in between the indicated testing days.

McNeill, 2009), and considering that SCH penetrates the blood-brain barrier and has an elimination half-life of approximately 25 min in rats (Bourne, 2001). In the PRB study, mice were administered SCH at 0.003 and 0.01 mg/kg or vehicle i.p. 10 min prior to testing in a volume of 5 mL/kg. The IGT and PRB studies were performed in a cross-over design because prior evidence supports for test-retest reliability in these paradigms (Milienne-Petiot et al., 2017). The BPM study was however, performed in a between-subject design due to rapid exploratory habituation seen in this task (Young et al., 2010). All mice received every dose over three different testing days with one day of regular training between testing days (operant tasks only). The order of treatment was randomly assigned. Each treatment day was separated by at least two days from the last treatment day. Mice were first tested in the IGT, then in the BPM, and finally in the PRB test (see Figure 1). In the PRB study lower doses of SCH were used because the highest dose used in the IGT and BPM studies resulted in lowered activity levels in mice. Thus, by decreasing the doses of SCH the effects on motivation would be directly related to effects of the drug and not to a decrease in activity impacting the capability of the mice to perform the task.

Apparatus

Fifteen five-hole operant chambers were used (25×25×25 cm, Med Associates Inc., St Albans, Vermont, USA), each of which consisted of a horizontal array of five square holes (2.5×2.5×2.5 cm) on a curved wall 2.5 cm above the grid floor, a food-delivery magazine (Lafayette Instruments, Lafayette, Indiana, USA) on the opposite panel at floor level, and a house light near the ceiling. Mice were trained to nosepoke to an illuminated light-emitting diode (LED) light recessed into the holes. The food-delivery magazine contained a well in which liquid reward (strawberry milkshake; Nesquik plus non-fat milk, 25 µL) was delivered by a peristaltic pump. Infrared beams were used to detect nosepoke responses and magazine entries. Chambers were enclosed in sound-attenuating boxes and ventilated by fans that also provided a low level of background noise. The control of stimuli and recording of responses were managed by a SmartCtrl Package 8-In/16-Out with additional interfacing by MED-PC for Windows (Med Associates Inc., St Albans, Vermont, USA) using custom programming.

Operant training and testing

Training and testing took place in 15 five-hole operant chambers (25×25×25 cm; Med Associates, St Albans, USA) for IGT and PRB. During the first training phase (Hab1), the reward area was illuminated every 15 s for 10 min while 30 µL strawberry milkshake (reward) was delivered. The number of collections was counted. Once at criterion (30 collections for two consecutive days), mice were moved to phase 2 (Hab2). For Hab2, four holes were lit and mice were required to nosepoke into one to obtain the reward. To minimize biased responses in specific holes, five consecutive nosepokes in one hole resulted in that hole being extinguished and inactive until two other holes were poked. The number of nosepokes for a reward were counted and criterion was set at >70 nosepokes for two consecutive sessions. Once responding consistently (on Hab2), mice were counter-balanced into three groups within each genotype based on response rate.

Single-session IGT

The IGT assesses risk-taking in rodents in a single session (Rivalan et al., 2009), to mimic the test used for humans. The details of the IGT have been given elsewhere (van Enkhuizen et al., 2014). In short, mice initiated a trial by nosepoking in the illuminated food magazine and then exiting it. After 5 s, four response holes were illuminated. After illumination, mice had 10 s to make a nosepoke response in one of four holes. Mice were rewarded with strawberry milkshake or punished with a time-out period depending on the reward/punishment schedule (see Figure 2). Two options delivered large rewards or long time-out penalties (disadvantageous), while the other two options delivered smaller rewards or shorter time-out penalties (advantageous). Risk-preference was measured as the percentage of advantageous choices (% Adv choices) across three trial blocks (total trials/three per animal), (advantageous/(disadvantageous+advantageous choices)*100) while within-session risk-learning (difference score), was measured as the difference between the % Adv choices

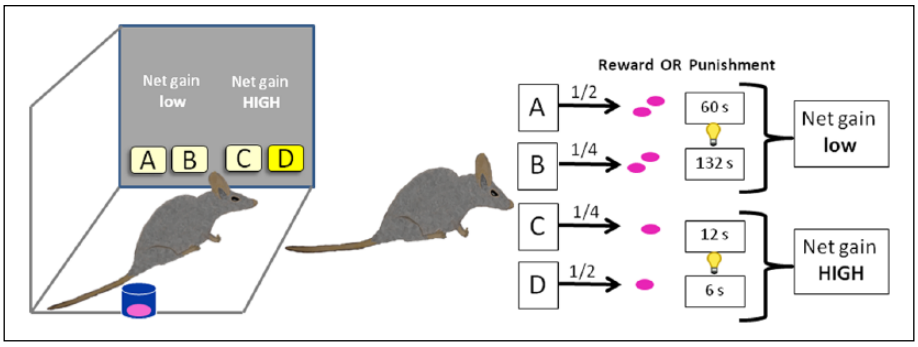

Figure 2. Schematic representation of the mouse Iowa Gambling Task. Mice were trained to nosepoke for a single reward. Then in a single test session, mice had four options resulting in varying reward (25 or 50 µL strawberry milkshake), and punishment (timeout with the chosen flashing light for varying durations) levels were altered. The ratios presented for each of the four options represent the probability of occurrence of punishment. Ultimately, as we previously demonstrated (van Enkhuizen et al., 2014), mice received the highest level of punishment and reward if the selected from options A and B, but the lowest reward and punishment if they selected from options C and D compared to options A and B that provide high levels of punishment.

Table 1. Description of the behavioral measures identified using a single-session mouse version of the Iowa Gambling Task (IGT).

Measures	Description
%Adv choices	Advantageous response options [(C+D)/total (A+B+C+D)]×100
% Disadvantageous choices	Disadvantageous response options [(A+B)/total (A+B+C+D)]×100
Difference score	Score difference in %advantageous choices over the course of the session (%Adv[T3]–%Adv[T1])
(*p*) Safe-stay	Probability of choosing advantageous options after being rewarded from advantageous options
(*p*) Risky-stay	Probability of choosing disadvantageous options after being rewarded from disadvantageous options
Omissions (%):	Failure to respond in any hole during the light stimulus duration of 12 s (motivation)
Premature responses (%)	Response in any cue hole during the 5-s inter-trial interval preceding illumination of the cue array (motor impulsivity)
Mean choice latency (s):	The latency to holepoke in one of the four holes (reaction time)
Mean collection latency (s):	The latency to collect a reward after a win

%Adv choices: percentage advantageous choices.

during trial block 3 – trial block 1. Using this metric, mice were identified as exhibiting high, intermediate, or low learn scores based on their difference from the mean. Safe, chance, and risk-preferring decision-makers were stratified as (a) >0.5, (b) between 0.5 and −0.5, and (c) <0.5 standard deviations from the mean respectively (consistent with previous reports; Milienne-Petiot et al., 2017; van Enkhuizen et al., 2014). The mice were stratified for each genotype separately. Responding prior to choice holes being illuminated were recorded as the percentage of premature (% Premature) responses of total trials, with trials restarting after a brief timeout period. Several other measures were recorded and presented such as safe stays and risky stays (see Table 1).

BPM

The BPM assesses exploratory behavior in rodents and has also been used in humans (Perry et al., 2009; Young et al., 2007). Locomotor behavior and exploration were examined in eight mouse BPM chambers (San Diego Instruments, USA) as described previously (Risbrough et al., 2006; van Enkhuizen et al., 2015b; Young et al., 2011a). In brief, each Plexiglas arena consists of a 30.5×61×38 cm area with three floor and eight wall holes (three in each long wall and one in each short wall; 1.25 cm in diameter, 1.9 cm from the floor), equipped with an infrared photobeam to detect holepoking. Each chamber is enclosed in an outer box with an internal white houselight above the arena (350 lux in the center and 92 lux in the four corners). A grid of 12×24 infrared photobeams 1 cm above the floor allowed for measurement of activity (2.5 cm apart; 24×12 X-Y array), recording the location of the mouse every 0.1 s, with its position defined across nine unequal regions (four corners, four walls, and center; Geyer et al., 1986). Another set of 16 photobeams, placed 2.5 cm above the floor was used to detect rearing behavior. The primary outcome measures were transitions across the defined regions and center entries (locomotor activity), holepoking and rearing (exploratory behavior), and spatial *d* (dimensionality of locomotor patterns). Spatial *d* measures the degree to which the animal makes more straight-line movements versus more circumscribed paths of movement, where a value closer to one reflects a one-dimensional straight path, and values closer to two indicating highly circumscribed small scale movements (Paulus and Geyer, 1991).

PRB test

The PRB test is one method to assay effortful motivation in rodents (Young and Markou, 2015), that is also used in humans (Wolf et al., 2014). During the 60 min PRB test, the mice had to

Table 2. Distribution of cohorts based on learn score by genotype for the Iowa Gambling Task (IGT).

Genotype	Safe-preferring mice	Indecisive mice	Risk-preferring mice
WT	6	14	9
KD	7	8	8

KD: knockdown; WT: wild-type.

make increasingly more nosepokes in the central lit stimulus aperture in order to get a food reward. The number of nosepokes required to gain a reward increased at each step according to the following progression: 1, 2, 4, 7, 11, 16, 22, 29, 37, 46, 56, and 67 (as described previously Milienne-Petiot et al., 2016; Young and Geyer, 2010; Young et al., 2011b). To maintain responding, the mice had to respond three times at each ratio before moving to the next, receiving one reward each time. The primary outcome measure of this task was the 'breakpoint', defined as the last ratio to be completed before the end of the session.

Statistics

We first confirmed that all data were distributed normally and displayed equal variances. Stable performance during training (Hab2) was assessed using a repeated measure analysis of variance (ANOVA) with days as a within-subject factor. The outcome measures for each experiment were analyzed using a one- or two-way ANOVA, with trial period and SCH/vehicle as within-subject factors, and learning score and genotype as between-subject variables. For the PRB study analysis, mice were excluded from analyses if total trials completed were zero or if the reaction times were more than two times the standard deviations above the mean (n=2). For the BPM study, drug treatment was analyzed as a between-subject factor. Tukey post-hoc analyses of statistically significant or relevant main and interaction effects were performed where applicable. The level of probability for statistical significance for primary outcome measures was set at 0.05. This level was corrected for secondary outcome measures using the Bonferroni correction method. All statistics were performed using SPSS (20.0, Chicago, USA) except for BPM analysis which was performed using the Biomedical Data Package statistical software (Statistical Solutions Inc., USA).

Results

Decision-making under risk-learning

The effects of SCH (0.01 mg/kg and 0.03 mg/kg) on DAT KD and WT performance of the IGT

Difference scores. There was no overall effect of genotype or learn score group on total trials completed. Additionally, no effect of genotype on difference scores were observed when mice were treated with vehicle, SCH at 0.01, or 0.03 mg/kg (drug by gene (F=2, not significant (n.s.))). As previously reported (Milienne-Petiot et al., 2017; van Enkhuizen et al., 2014), however, risk-learning was gauged by the difference score of %Adv choices between trial period 3 minus trial period 1, analyzed by genotype within each learn score group (safe-preferring (SP), indecisive (IND), and risk-preferring (RP); see also Table 2). There was a drug by genotype by performing group interaction ($F_{(4,94)}$=3.5, p<0.05). For SP mice, there was a main effect of genotype on difference score (%Adv choices) when treated with vehicle ($F_{(1,11)}$=5.2, p<0.05), revealing that KD mice exhibited lower scores than WT mice consistent with our previous findings (Milienne-Petiot et al., 2017).

There was a main effect of drug treatment ($F_{(2,22)}$=7.5, p<0.01) but no interaction with genotype (F<1, n.s.). Mice treated with SCH at 0.01 mg/kg and 0.03 mg/kg had significantly lower difference scores compared to vehicle treated mice (p<0.05 and p<0.01 respectively), although both doses did not differ from each other. For IND mice, there was no statistically significant effect of genotype on difference score when treated with vehicle (F<1, n.s.). There was no main effect of drug (F<1, n.s.), but there was a genotype by drug interaction ($F_{(2,42)}$=5.9, p<0.01). IND DAT KD mice had a higher difference score than WT mice (p=0.06) when treated with SCH at 0.01 mg/kg, while both genotypes had equal difference scores when treated with SCH at 0.03 mg/kg. Finally, there was a main effect of genotype in RP mice when treated with vehicle ($F_{(1,15)}$=6.4, p<0.05), revealing that KD mice exhibited lower scores than WT mice. There was a main effect of drug ($F_{(2,30)}$=4.9, p<0.05) and a trend towards a statistically significant interaction between genotype and drug ($F_{(2,30)}$=3.1, p=0.06). Mice treated with SCH at 0.01 mg/kg had a significantly higher difference score compared to vehicle treatment but this was irrespective of genotype (p<0.05). SCH treatment at 0.03 mg/kg did not result in a significantly different difference score compared to vehicle or SCH at 0.01 mg/kg. These findings are depicted in Figure 3. The difference in %Adv choices in trial period 3 tended to be higher in WT mice compared to KD mice treated with saline in SP mice ($F_{(1,11)}$=3.0, p=0.1). The more risk-preferring performance of KD mice is consistent with findings of earlier studies (van Enkhuizen et al., 2014).

Safe-preferring mice – win-stay/lose-shift strategies. In SP mice, there was no main effect of drug (F=1.4, n.s.), or genotype (F=2, n.s.) on safe-stays. A main effect of trial period on safe-stay ($F_{(2,22)}$=7.3, p<0.005), but no interaction with genotype (F=2.4, n.s.), was observed (see Figure 4(a)). Post-hoc analyses revealed that mice increased their safe-stays during the last compared with the first trial blocks (p<0.01). A main effect of drug ($F_{(2,22)}$=7.2, p<0.005), and trial period ($F_{(2,22)}$=11.4, p<0.001), on risky-stays was observed in WT and KD mice. Although there was a trend towards a statistically significant main effect of genotype ($F_{(1,11)}$=3.6, p=0.08), there was no interaction between drug and genotype (F<1, ns), nor an interaction between genotype and trial period (F<2, n.s.). There was however, an interaction between trial period and drug ($F_{(4,44)}$=3.2, p<0.05), an effect that did not pass a Bonferroni correction (p<0.005). Post-hoc analyses revealed that mice when treated with SCH 0.01 mg/kg made significantly fewer risky-stays compared to vehicle and SCH 0.03 mg/kg treatments (p<0.01 and p<0.05 respectively). Mice significantly decreased the risky-stays over the course of the session (p<0.01) but this decrease was less pronounced when mice were treated with SCH at the highest dose (Figure 4(b)).

Safe-preferring mice– secondary measures. A main effect of drug on %premature responses ($F_{(2,22)}$=3.9, p<0.05) but no main effect of trial period (F<1, n.s.) was observed.

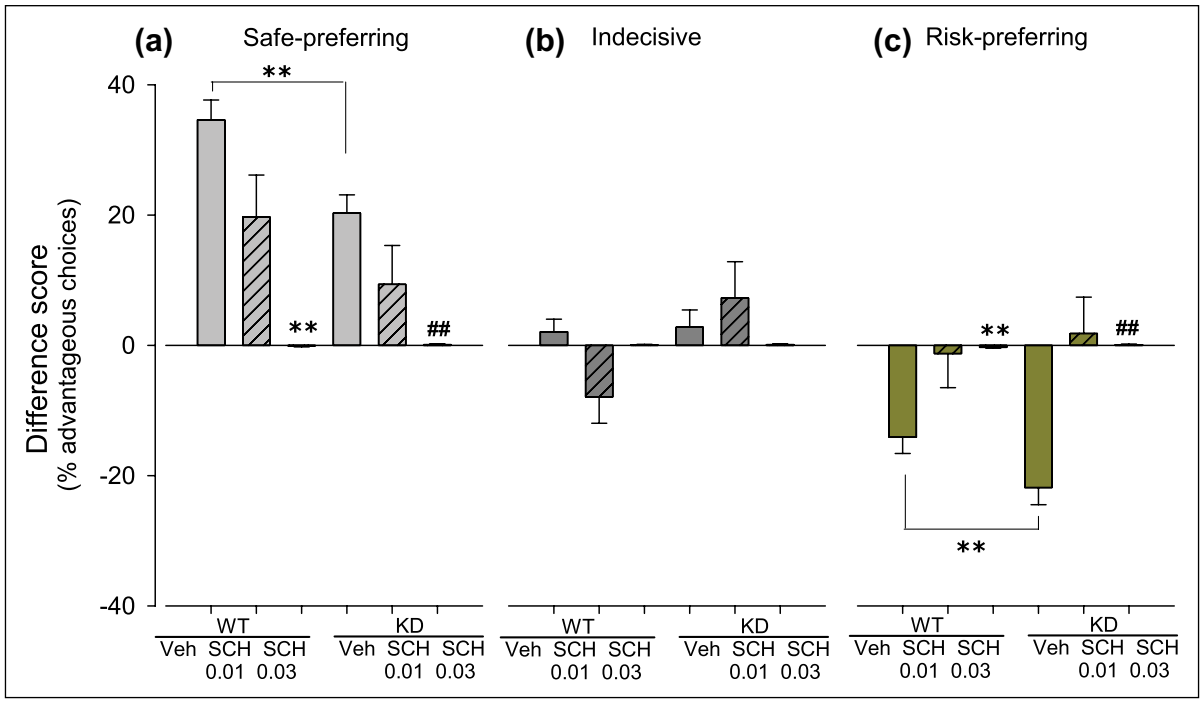

Figure 3. Effects of acute SCH 23390 hydrochloride (SCH) on the percentage advantageous difference score (%Adv) of dopamine transporter (DAT) wild-type (WT) and knockdown (KD) mice. Data are presented in terms of learning over a single session. The performance of mice in the Iowa Gambling Task (IGT) was categorized by their learning score (%Adv from trial period 3 minus trial period 1). Some mice exhibited a safe preferring learning score (a), some showed no change over time (b), while some exhibited a preference for the risky side (c). Safe-preferring KD mice chose significantly less from the advantageous choices compared to WT mice. Risk-preferring KD mice selected significantly more from the disadvantageous choices compared to WT mice. SCH treatment reduced the positive change score of safe-preferring WT and KD mice, while also reducing the negative change score of risk-preferring WT and KD mice. There was no effect of treatment on indecisive mice. Data are presented as mean±standard error of the mean (SEM). $^{**}p<0.01$ compared with vehicle (Veh)-treated WT mice; $^{\#\#}p<0.01$ compared with Veh-treated KD mice.

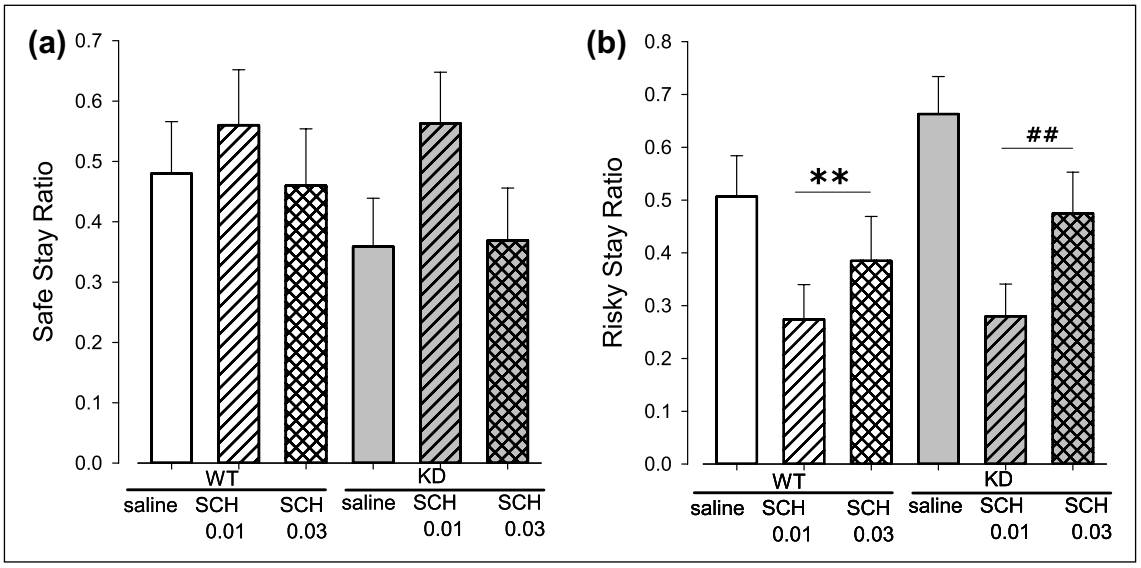

Figure 4. Effects of acute SCH 23390 hydrochloride (SCH) on strategy measures of dopamine transporter (DAT) wild-type (WT) and knockdown (KD) mice. DAT KD mice exhibited behaviors on the secondary outcome measures of the Iowa Gambling Task (IGT) that were consistent with previous reports (van Enkhuizen et al., 2014). One of the secondary measures was a reduction in the likelihood of repeating a response at the safe side after being rewarded at that side (a). SCH treatment had no significant effect on this measure in neither WT nor KD mice. Drug treatment had a lowering effect on staying at the risky side after a reward was received at that side (b). Data are mean±standard error of the mean (SEM). $^{**}p<0.01$ compared with WT mice treated with vehicle; $^{\#\#}p<0.01$ compared with KD vehicle-treated mice.

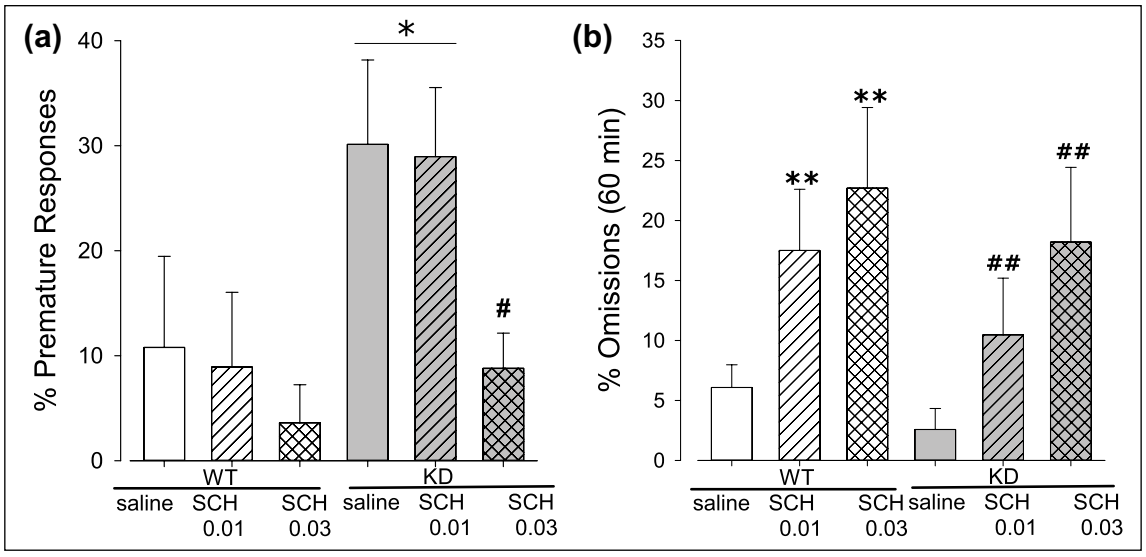

Figure 5. Effects of acute SCH 23390 hydrochloride (SCH) on secondary outcome measures of safe-preferring dopamine transporter (DAT) wild-type (WT) and knockdown (KD) mice in the Iowa Gambling Task (IGT) study. DAT KD mice exhibited behaviors on the secondary outcome measures that were consistent with previous reports (van Enkhuizen et al., 2014). These behaviors included increased percentage premature responses (a). SCH treatment exerted a main effect of lowering percentage premature responses irrespective of genotype, although post-hoc analyses revealed significant effects in KD mice only at the highest dose. DAT WT and KD exhibited comparable percentage omissions (%Omissions) when treated with saline and both groups displayed increased %Omissions when treated with SCH (b). Data are mean±standard error of the mean (SEM). *p<0.05 and **p<0.01 compared with WT mice; #p<0.05 and ##p<0.01 compared with DAT KD mice treated with vehicle.

There was a main effect of genotype on this measure ($F_{(1,11)}$=5.1, p<0.05). No interactions were observed. Post-hoc analyses revealed that DAT KD mice exhibited significantly decreased premature responses when treated with SCH at 0.03 mg/kg (p<0.05) compared to vehicle treatment (see Figure 5(a)). There was a main effect of drug ($F_{(2,22)}$=6.2, p<0.01), and trial period ($F_{(2,22)}$=4.4, p<0.05), on percentage omissions (%Omissions) but there was no effect of genotype, nor any interactive effects (F<2, n.s.). Post-hoc analyses revealed that mice made significantly more %Omissions when treated with SCH at 0.01 or 0.03 mg/kg compared to treatment with vehicle (p<0.01 and p<0.05 respectively) irrespective of genotype (see Figure 5(b)). Given the Bonferroni correction required for multiple comparisons (p<0.005), none of these drug or genotype effects reached statistical significance.

An overview of all secondary measures displayed per learn score group is presented in Table 3.

Exploration and activity in the BPM

The effects of SCH (0. 01 mg/kg and 0.03 mg/kg) were examined on DAT KD and WT mice in the BPH.

Locomotor behavior. A main effect of genotype on transitions was observed ($F_{(1,48)}$=35.6, p<0.01; Figure 6(a)) as DAT KD mice made significantly more transitions than WT mice when treated with vehicle. There was also a main effect of drug ($F_{(2,48)}$=35.6, p<0.01) in which the highest dose of SCH significantly decreased transitions compared to vehicle treatment (p<0.05) in both DAT KD and WT mice. Additionally, a trend towards an interaction between genotype and drug ($F_{(2,48)}$=2.9, p=0.067) was observed. Post-hoc analyses revealed that DAT KD mice made significantly more transitions than WT mice irrespective of treatment. While only the highest doses of SCH significantly decreased transitions in WT mice (p<0.01), in DAT KD mice both doses of SCH (0.01 and 0.03 mg/kg) significantly reduced transitions (p<0.05 and p<0.01 respectively). A dose-dependent effect can be seen for this measure as DAT KD treated with SCH at 0.01 mg/kg made more transitions than mice treated with SCH at 0.03 mg/kg (p<0.05).

Secondly, no main effect of genotype on center entries could be observed (F<3, n.s.) but SCH significantly decreased the number of center entries made by DAT KD and WT mice ($F_{(2,48)}$=19.5, p<0.01; Figure 6(b)). There was no interaction between genotype and treatment (F<1, n.s). Post-hoc analyses revealed that DAT WT mice treated with SCH at 0.03 mg/kg made significantly fewer center entries compared to WT mice treated with vehicle (p<0.01). DAT KD mice treated with vehicle made significantly more center entries compared to KD mice treated with SCH at 0.01 mg/kg (p<0.05) or SCH at 0.03 mg/kg (p<0.01).

Specific exploratory behavior. There was no effect of genotype (F<1, n.s.; Figure 6(c)) nor interaction between genotype and drug treatment (F<1, n.s.) for the number of holepokes but there was a main effect of drug treatment ($F_{(2,48)}$=13.4, p<0.01) as SCH lowered the number of pokes. Bonferroni correction for multiple comparison (p<0.005), meant however that this finding was no longer significant. Post-hoc analyses, however revealed that DAT KD mice treated with SCH at 0.03 mg/kg significantly reduced holepoking compared with those treated with vehicle (p<0.01). DAT KD mice exhibited increased rearing compared to WT mice ($F_{(1,48)}$=6.2, p<0.05; Figure 6(d)), while treatment with

Table 3. Overview of secondary measures for the Iowa Gambling Task (IGT).

Geno-type	Learn score	Drug	Safe stay	Risky stay	Omission %	Premature responses %	Mean choice latency	Mean collection latency
WT	SP	Veh	0.48 (0.12)	0.51 (0.13)	6.09 (4.85)	10.79 (7.05)	3.80 (0.54)	1.11 (0.11)
		SCH 0.01	0.56 (0.12)	0.27 (0.10)	17.51 (6.82)	8.94 (6.58)	4.22 (0.50)	1.41 (0.54)
		SCH 0.03	0.46 (0.11)	0.39 (0.11)	22.70 (10.00)	3.62 (4.86)	4.96 (0.54)	2.14 (1.03)
	IND	Veh	0.30 (0.07)	0.58 (0.08)	14.02 (3.07)	6.47 (4.61)	4.32 (0.34)	1.28 (0.07)
		SCH 0.01	0.48 (0.08)	0.32 (0.06)	24.53 (4.32)	3.55 (4.31)	4.48 (0.31)	1.48 (0.34)
		SCH 0.03	0.30 (0.07)	0.37 (0.07)	33.21 (6.32)	6.26 (3.18)	5.14 (0.34)	2.70 (0.65)
	RP	Veh	0.41 (0.10)	0.45 (0.10)	17.98 (3.96)	2.77 (5.75)	4.62 (0.44)	1.31 (0.09)
		SCH 0.01	0.33 (0.10)	0.39 (0.08)	26.35 (5.57)	5.38 (5.37)	5.56 (0.41)	2.60 (0.44)
		SCH 0.03	0.43 (0.09)	0.25 (0.09)	49.53 (8.16)	0.45 (3.96)	5.60 (0.44)	2.29 (0.84)
KD	SP	Veh	0.36 (0.11)	0.66 (0.12)	2.59 (4.49)	30.14 (6.53)	3.41 (0.50)	0.98 (0.10)
		SCH 0.01	0.56 (0.11)	0.28 (0.09)	10.48 (6.32)	28.97 (6.09)	3.21 (0.46)	2.01 (0.50)
		SCH 0.03	0.37 (0.10)	0.48 (0.10)	18.21 (9.26)	8.80 (4.50)	5.16 (0.50)	1.78 (0.96)
	IND	Veh	0.40 (0.10)	0.50 (0.11)	6.29 (4.20)	21.80 (6.10)	3.93 (0.46)	1.17 (0.10)
		SCH 0.01	0.42 (0.11)	0.54 (0.09)	15.20 (5.91)	12.67 (5.70)	4.81 (0.43)	1.41 (0.47)
		SCH 0.03	0.50 (0.09)	0.38 (0.10)	18.18 (8.66)	23.15 (4.21)	4.27 (0.47)	1.33 (0.89)
	RP	Veh	0.48 (0.10)	0.45 (0.11)	8.73 (4.20)	30.40 (6.10)	3.69 (0.46)	1.16 (0.10)
		SCH 0.01	0.41 (0.11)	0.62 (0.09)	5.29 (5.91)	32.64 (5.70)	3.35 (0.43)	1.00 (0.47)
		SCH 0.03	0.43 (0.09)	0.42 (0.10)	18.14 (8.66)	12.21 (4.21)	4.15 (0.47)	3.05 (0.89)

IND: indecisive; KD: knockdown; RP: risk-preferring; SCH: SCH 23390 hydrochloride; SP: safe-preferring mice; Veh: vehicle treatment; WT: wild-type.
SCH 0.01 dose at 0.01 mg/kg; SCH 0.03 dose at 0.03 mg/kg. Data presented as mean (standard error of the mean (SEM)).

SCH decreased rearing in all mice ($F_{(2,48)}$=13.0, p<0.01), with no interaction between drug and genotype (F<1, ns.). Again however, Bonferroni correction limits the significance of this finding. Post-hoc analyses revealed that WT mice treated with SCH at 0.03 mg/kg reared significantly less than mice treated with vehicle (p<0.05). Similarly, SCH at 0.03 mg/kg lowered rearing in DAT KD mice compared with vehicle-treated KD mice (p<0.05).

Locomotor patterns. Overall, DAT KD mice exhibited lower spatial *d* compared to WT mice ($F_{(1,48)}$=4.7, p<0.05; Figure 6(e)). A main effect of drug treatment ($F_{(2,48)}$=20.7, p<0.01), and an interaction ($F_{(2,48)}$=4, p<0.05) with genotype was also observed, although neither are significant following a Bonferroni correction (p<0.005). Post-hoc analyses revealed that SCH-treated DAT KD mice (0.03 mg/kg) exhibited higher spatial *d* compared to SCH (0.01 mg/kg) and vehicle-treated DAT KD mice. Interestingly, DAT KD treated with SCH at 0.03 mg/kg exhibited significantly higher spatial *d* compared to WT mice treated with vehicle (p<0.01).

Effortful motivation

Effects of SCH (0.01 mg/kg and 0.003 mg/kg) in DAT KD and WT mice in the PRB test. DAT KD mice exhibited significantly higher breakpoints compared to WT mice ($F_{(1,53)}$=10.5, p<0.01; Figure 7). SCH treatment reduced breakpoint in DAT KD and WT mice ($F_{(2,53)}$=5.0, p<0.01). There was a trend towards a statistically significant interaction between drug and genotype ($F_{(2,53)}$=2.8, p=0.06). Post-hoc analyses revealed that WT mice treated with SCH at 0.01 mg/kg exhibited a significantly lower breakpoint compared to vehicle-treated WT mice (p<0.01). Vehicle-treated DAT KD mice exhibited significantly higher breakpoints compared to vehicle-treated WT mice (p<0.05). Also, SCH-treated DAT KD mice (0.003 mg/kg) exhibited significantly higher breakpoints compared to vehicle-treated DAT KD mice (p<0.01).

Discussion

Consistent with our hypothesis and previous observations, male DAT KD mice exhibited a risk-preference profile (lower percentage of advantageous choices) and motoric impulsivity (higher percentage of premature responses) in the IGT compared to their WT littermates (Milienne-Petiot et al., 2017; van Enkhuizen et al., 2014). Additionally, DAT KD mice exhibited higher effortful motivation (breakpoint; Cagniard et al., 2006a,b; Milienne-Petiot et al., 2016), and hyperexploratory behavior (increased activity and rearing; Perry et al., 2009; Milienne-Petiot et al., 2017; van Enkhuizen et al., 2015a). Hence, DAT KD mice exhibited a mania-relevant profile across multiple domains. Systemic dopamine D_1-family receptor blockade (via SCH treatment) reduced the preference for both the advantageous or disadvantageous choices of DAT KD and WT mice to chance levels. Also, irrespective of genotype, treatment with the dopamine D_1-family receptor antagonist SCH reduced activity and exploration of mice in the BPM. SCH treatment at 0.003 mg/kg further increased effortful motivation in DAT KD mice compared to vehicle treatment; an effect that was not seen in WT mice. Conversely, SCH treatment at 0.01 mg/kg decreased effortful motivation in DAT WT mice while having no effect on DAT KD mice compared to vehicle treatment. These data support the hypothesis that dopamine D_1-family receptors likely play a downstream role of the mania-relevant behaviors of male DAT KD mice, albeit that these receptors are important in each of these behaviors in normal mice

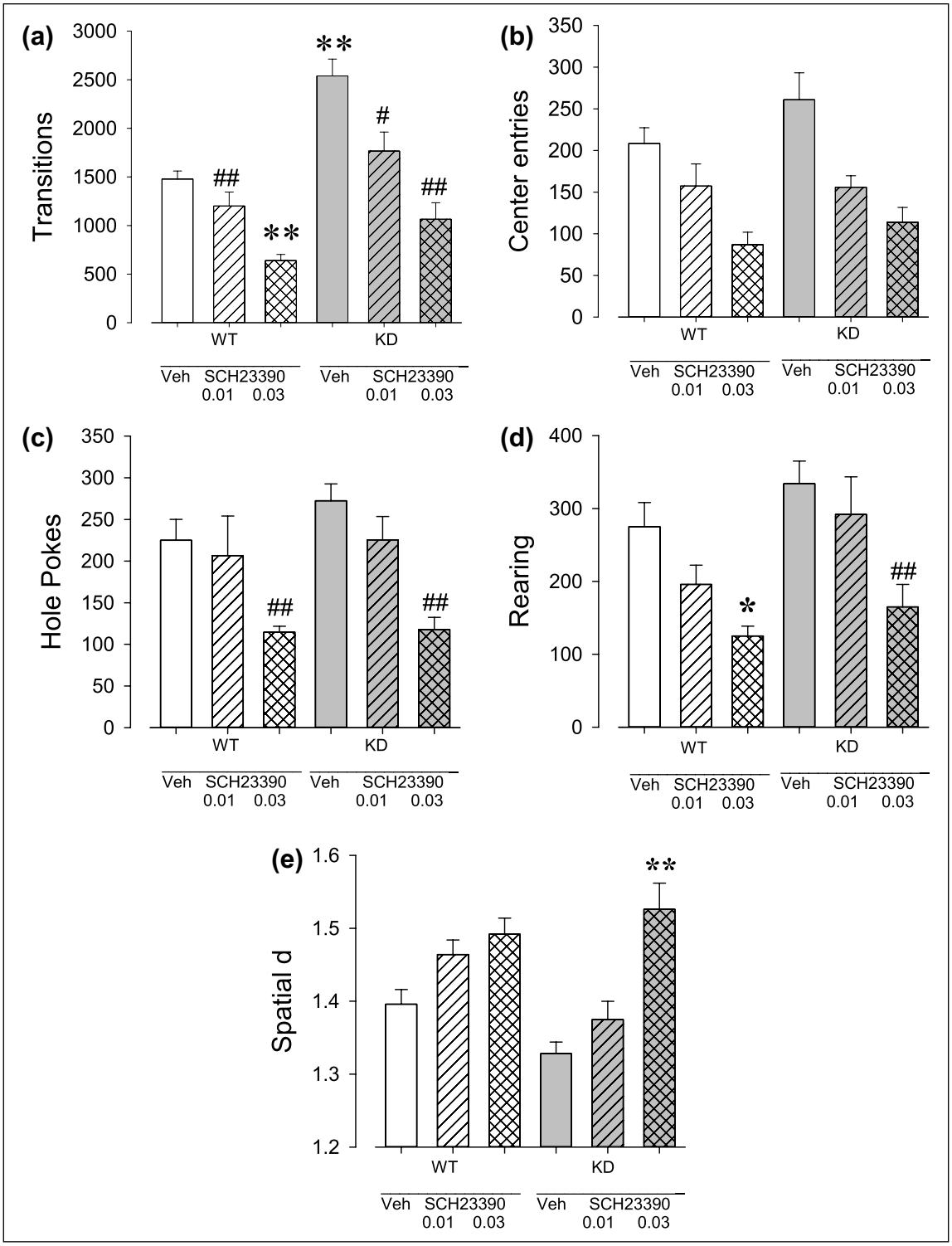

Figure 6. Effects of acute SCH 23390 hydrochloride (SCH) on activity and exploration measures in dopamine transporter (DAT) wild-type (WT) and knockdown (KD) mice tested in the Behavioral Pattern Monitor (BPM). DAT KD mice exhibited behaviors in the BPM that were consistent with previous reports (Young et al., 2007). These behaviors included increased transitions (a), increased center entries (b), increased holepokes (c) and rearing (d). On the other hand, spatial *d* was not significantly different for DAT KD compared to WT mice when treated with vehicle (e). SCH treatment attenuated these behaviors in DAT KD while also reducing activity and exploration in WT mice. Data are mean±standard error of the mean (SEM). $^{*}p<0.05$ and $^{**}p<0.01$ compared with WT mice; $^{\#}p<0.05$ compared with DAT KD mice treated with vehicle.

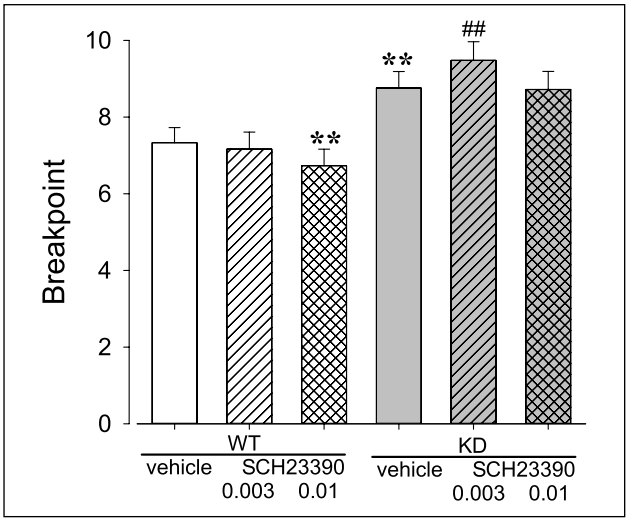

Figure 7. Effects of acute SCH 23390 hydrochloride (SCH) on effortful motivation (breakpoint) in dopamine transporter (DAT) knockdown (KD) and wild-type (WT) mice tested in the Progressive Ratio Breakpoint test. DAT KD mice displayed higher breakpoint compared to WT mice when treated with vehicle. SCH treatment significantly decreased breakpoint in WT mice only. Data are mean±standard error of the mean (SEM). $^{**}p<0.01$ compared with WT mice; $^{\#\#}p<0.01$ compared with DAT KD mice treated with vehicle.

also. Confirmation of these effects in females is still required for further generalization. Importantly, DAT KD mice that exhibit BD mania-relevant behaviors demonstrate altered sensitivity to this dopamine D_1-family receptor antagonist on only some behaviors compared with their WT littermates, limiting support for this mechanism as a treatment for BD.

Effects of dopamine D_1-family receptor antagonism on decision-making in DAT KD mice

The current study replicates earlier observations that DAT KD mice exhibited impaired decision making in the IGT compared to WT mice (Milienne-Petiot et al., 2017; van Enkhuizen et al., 2014), a profile consistent with patients with BD mania (Adida et al., 2008; van Enkhuizen et al., 2014). When treated with SCH, both safe-preferring DAT KD and WT mice decreased their selection of advantageous choices to chance levels, while risk-preferring mice increased their selection to chance levels. Moreover, dopamine D_1-family receptor blockade did not improve safe-stay behavior in either group. Thus, systemic dopamine D_1-family receptor blockade does not specifically treat the risky decision making impairments seen in DAT KD mice, and may impair decision-making altogether. This profile is similar to that observed in a previous study using DAT KD and WT treated with a serotonin-dopamine modulator, brexpiprazole, with antagonistic activity at the dopamine $D_{2/3}$ receptors (Milienne-Petiot et al., 2017). These results seem to be in contrast with previous findings indicating that systemic D_1- and/ or D_2-receptor blockade in rats resulted in a reduction of risky choice in a risk discounting task in normal rats (St Onge and Floresco, 2009). The risk discounting task and the IGT differ however, in that the former delivers a (small) certain reward while the IGT includes uncertainty and punishment likely involving a different interplay of neuronal systems to modulate reward and punishment learning (Orsini et al., 2015). It is nevertheless possible that blockade of dopamine D_1-family receptor in specific regions of the brain, e.g. in the amygdala (Larkin et al., 2016), or prefrontal cortex (St Onge et al., 2011), could yield a more treatment-specific effect in DAT KD mice.

Patients with BD mania exhibit impulse control deficits (McElroy et al., 1996), behaviors that may be harmful to the individual or others. Given that premature responses may measure an aspect of motoric impulsivity (Dalley et al., 2002), potentially impacted by temporal perception (Cope et al., 2016), which is sped in BD mania, it is important to note that DAT KD mice exhibited higher premature responses compared to WT mice, consistent with previous observations (Milienne-Petiot et al., 2017; van Enkhuizen et al., 2014). Dopamine D_1 receptors have previously been implicated in premature responses in rats (van Gaalen et al., 2006). Given that SCH treatment remediated the increased premature responses of DAT KD mice, the present findings provide some potential support for the systemic dopamine D_1-family receptor blockade in the treatment of BD mania behaviors.

This dopamine D_1-family receptor-induced attenuation of elevated premature responses is consistent with a dopamine D_1 receptor blockade attenuating amphetamine-induced elevated premature responses in rats performing a gambling task, although the blockade did not alter the effects of amphetamine on this learned decision-making (Zeeb et al., 2013). The lack of dopamine D_1 receptor antagonism effects on decision-making in Zeeb and colleagues (2013) could therefore result from rats being well-trained while the current study investigated within-session risk-learning. Differences between within-session vs learned decision-making behavior was seen previously, whereby DAT blockade increased safe-choices in trained rats, but increased risk-choices in mice undergoing learning (Orsini et al., 2015; van Enkhuizen et al., 2014; Zeeb et al., 2009). The dopamine D_1 receptors have been heavily implicated in numerous forms of learning (Acheson et al., 2013; El-Ghundi et al., 1999; Matthies et al., 1997; Wolf et al., 2014; Young and Geyer, 2010), with recent evidence demonstrating suppression of striatal dopamine D_1 receptors negatively impact reward associative learning (Higa et al., 2017). Hence, dopamine D_1 receptor-blockade negatively affecting risk-learning may relate more to the need of dopamine D_1 receptor for learning and not risk-preference specifically. Irrespective of their role in risk-learning however, dopamine D_1-family receptor antagonism may ameliorate waiting impulsivity deficits and therefore possibly prove helpful as a targeted treatment option.

Effects of dopamine D_1-family receptor blockade on exploration and activity in DAT KD

The current findings replicate observations that DAT KD mice exhibit a hyperexploratory behavioral profile consistent with patients with BD mania (increased activity and specific exploration while displaying more linear patterns of movement; Perry et al., 2009 and Young et al., 2010). Earlier evidence using dopamine D_1 receptor knockout mice demonstrated a role for this receptor in mediating the effects of DAT inhibitor (modafinil) in the BPM (Young et al., 2011a). Dopamine D_1 knockout mice did

not show the modafinil-induced increase in activity (transitions) or specific exploration (holepokes and rearing) that was observed in WT mice or in the other dopamine receptor knockout mice (D_2, D_3, or D_4). In the same study, SCH attenuated the modafinil-induced increases in activity and specific exploration (holepokes) although this attenuation was not specific. In a different study, SCH-induced dopamine D_1-family receptor blockade reduced activity in rats and mice (Clausen et al., 2011), effects replicated in this current study. SCH decreased the hyperactivity and specific exploration of DAT KD mice as well as attenuated their more circumscribed pattern of movement in a dose-related manner. In contrast with chronic valproate and lithium treatment, dopamine D_1-family receptor blockade affected each aspect of hyperactivity of DAT KD mice, while affecting WT mice similarly. Hence, the dopamine D_1-family receptor likely plays an important role in mediating normal exploratory behavior. Such treatments could prove to be a potential short-term therapeutic for hyperactivity in BD mania, especially if other behavioral aspects are not negatively impacted by such a treatment.

Effects of dopamine D_1-family receptor antagonism on effortful motivation in DAT KD

Abnormally high effortful motivation (goal-seeking behavior) is a symptom seen in BD mania (Fulford et al., 2015; Johnson, 2005). The present study supports previous observations that mice with reduced DAT expression exhibited increased effortful motivation as measured by breakpoint (Cagniard et al., 2006a; Milienne-Petiot et al., 2016; Sommer et al., 2014). Previous studies have linked the dopamine D_1 receptor to appetitive stimuli and motivation (Higa et al., 2017; Wessa et al., 2014). These effects in normal animals are consistent with dopamine D_1-family receptor blockade-induced inhibition of the motivational properties of stimuli induced by drugs of abuse (Acquas et al., 1989; Eiler et al., 2003). The present study however, showed that dopamine D_1-family receptor blockade did not attenuate the heightened motivation of DAT KD mice, despite the blockade reducing breakpoint as observed in WT mice. In fact, the lowest dose of SCH actually elevated the breakpoint of DAT KD mice. It is unclear what drove this result since SCH is a selective antagonist of dopamine D_1-family receptors and the level of postsynaptic dopamine D_1 receptor (drd1) expression has been reported to be similar between DAT KD and WT mice (Zhuang et al., 2001). Thus, it was unlikely that this increased sensitivity to dopamine D_1 receptor blockade was due to a lower level of drd1 expression. Also, the doses used in this study were low enough not to produce effects on overall activity in mice since they were lower than the dose that produced reduction in activity as measured in the BPM. Earlier studies found that lithium treatment also increased breakpoint in DAT KD mice compared to vehicle (Milienne-Petiot et al., 2016) while lithium attenuated the elevated breakpoint of mice treated GBR12909 (pharmacological inhibition of DAT functioning). It has been reported that the dopamine D_2 receptor function is altered in DAT KD compared to WT mice (Wu et al., 2007), and this could also be the case for dopamine D_1 receptor function (Zhuang et al., 2001). As D_2 receptors have been reported to play a critical role in the regulation of glutamatergic activity in the corticostriatal pathway, downregulation of these receptors may lead to increased glutamatergic function which may translate to changes in salience and motivation (Wu et al., 2007). It is also possible, that administration of dopamine D_1-family receptor antagonists in specific regions may decrease breakpoint in DAT KD mice. For example, administration of dopamine D_1 receptor antagonist in the nucleus accumbens caused a reduction in breakpoint for cocaine reward (McGregor and Roberts, 1993, 1995; Nicola and Deadwyler, 2000). Blockade of dopamine D_1-family receptor by systemic administration did not attenuate the elevated motivation in DAT KD mice in the current study and therefore reduces support for the dopamine D_1 receptor as a target for the treatment of heightened goal-seeking behavior.

Conclusions

DAT KD mice exhibit a behavioral profile consistent with mania: hyperactivity, increased exploration, straighter patterns of movement, hypermotivation, and increased risk-taking, as well as increased premature responding. Blockade of dopamine D_1-family receptors attenuated the mania relevant profile of DAT KD mice by decreasing activity, exploration, and risk-taking, although similar effects were observed in DAT WT mice. Importantly, impulsivity, or premature responding, was reduced in DAT KD mice and WT mice. Thus, the dopamine D_1-family receptors seem to be involved in the mechanisms of the impulsivity behavioral profile and are also likely involved in activity, exploration, and risk-taking in DAT KD and WT mice alike. Blockade of the D_1-family receptors could prove useful to attenuate those behaviors and remediate impulsivity, although the increase in motivation as seen in DAT KD mice further limits the suitability of such downstream blockade as a potential treatment in BD mania. An indirect modulation of the dopamine D_1-family receptors could prove a better treatment target.

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