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Reduced Dopamine Transporter Functioning Induces High-Reward Risk-Preference Consistent with Bipolar Disorder

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Individuals with bipolar disorder (BD) exhibit deleterious decision making, negatively impacting their lives. Such aberrant decision making can be quantified using the Iowa Gambling Task (IGT), which requires choosing between advantageous and disadvantageous options based on different reward/punishment schedules. The mechanisms underlying this behavioral deficit are unknown, but may include the reduced dopamine transporter (DAT) functioning reported in BD patients. Using both human and mouse IGTs, we tested whether reduced DAT functioning would recreate patterns of deficient decision making of BD patients. We assessed the IGT performance of 16 BD subjects (7 female) and 17 healthy control (HC) subjects (12 female). We recorded standard IGT performance measures and novel post-reward and post-punishment decision-making strategies. We characterized a novel single-session mouse IGT using C57BL/6J mice ($n = 44$). The BD and HC IGT performances were compared with the effects of chronic (genetic knockdown (KD; $n = 31$) and wild-type ($n = 28$) mice) and acute (C57BL/6J mice ($n = 89$) treated with the DAT inhibitor GBR12909) reductions of DAT functioning in mice performing this novel IGT. BD patients exhibited impaired decision making compared with HC subjects. Both the good-performing DAT KD and GBR12909-treated mice exhibited poor decision making in the mouse IGT. The deficit of each population was driven by high-reward sensitivity. The single-session mouse IGT measures dynamic risk-based decision making similar to humans. Chronic and acute reductions of DAT functioning in mice impaired decision-making consistent with poor IGT performance of BD patients. Hyperdopaminergia caused by reduced DAT may impact poor decision making in BD patients, which should be confirmed in future studies.

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INTRODUCTION

Several psychiatric disorders are associated with impaired decision making (Christodoulou *et al*, 2006; Fond *et al*, 2013; Mantyla *et al*, 2012), deleteriously impacting the patients' quality of life (Jollant *et al*, 2007). Neural networks contributing to decision making have been identified (Floresco *et al*, 2008; Lin *et al*, 2008). Clarification of the mechanism(s) underlying decision making in psychiatric patients requires delineation for targeted therapeutic development. The Iowa Gambling Task (IGT) utilizes high-yield/high-risk *versus* low-yield/low-risk options to measure decision making with real-world translational validity in one test-session (Bechara *et al*, 1994). Patients with bipolar disorder (BD) exhibit poor IGT performance (Adida *et al*, 2011; Ibanez *et al*, 2012). Moreover, a diagnosis-specific performance profile can be discerned. Manic BD patients are hypersensitive to rewards (Cassidy *et al*, 1998). Schizophrenia patients exhibit disrupted contingency learning (Brambilla *et al*, 2012), whereas depressed patients are more sensitive to punishment (Adida *et al*, 2011; Must *et al*, 2013). Collectively, these findings support differing mechanisms underlying poor decision making in these disorders.

Model animals for these impairments are required for treatment development (Insel, 2007). Based on the human IGT, animal analogs have been created (de Visser *et al*, 2011). In the rodent IGT, animals are presented with four options with different reward/punishment probabilities and magnitudes. Consistent with the human IGT, two options offer small rewards and little punishment (safe/advantageous choices), whereas the other two options offer larger rewards and more punishment (risky/disadvantageous choices). The effects of dopaminergic, serotonergic, and noradrenergic manipulations have been investigated in rats and mice using a rodent IGT, in which learning was acquired and examined across multiple test sessions (Baarendse *et al*, 2013; van Enkhuizen *et al*, 2013b; Zeeb *et al*, 2009; Zeeb *et al*, 2013). These studies revealed various neurotransmitter involvements on *already learned* decision-making processes. In contrast to these tasks, however, the human IGT examines dynamic decision-making *during*

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learning in a single session, limiting the translational validity of multiple session rodent IGT studies (de Visser *et al*, 2011). In support of this assertion, similar experimental manipulations in multiple- *vs* single-session rodent IGTs produced different results. Orbitofrontal cortical lesions exaggerated deficits of rats in within-session (Rivalan *et al*, 2011) but not learned (Zeeb and Winstanley, 2011) rat decision-making in single- *vs* multiple session IGTs, respectively. In the single-session rodent IGT, good, intermediate, and poor decision-making rodents can be identified based on their risk-learning performance (Rivalan *et al*, 2009). Inter-individual differences are also observed among healthy humans performing the IGT (Bechara and Damasio, 2002a; Weller *et al*, 2010). Assessment of mechanisms that may contribute to impaired IGT performance in BD could therefore be conducted in mice by using a single-session IGT that enables direct comparisons with human IGT findings.

Although mechanisms underlying BD symptoms remain poorly defined, increasing evidence suggests that elevated dopamine (DA) levels most likely have a key role (Manji *et al*, 2003; Vawter *et al*, 2000). One key mechanism of DA homeostasis is its reuptake from the synaptic cleft into presynaptic nerve terminals by the DA transporter (DAT). Because several studies support an important role of DA in regulating risk-based decision making in rodents (Floresco *et al*, 2008; St Onge and Floresco, 2009), altered DAT functioning may contribute to abnormal decision making in individuals with BD. Supporting this assumption, polymorphisms in the *DAT* gene have been linked with BD (Greenwood *et al*, 2006; Pinsonneault *et al*, 2011), likely lowering functional DAT levels (Horschitz *et al*, 2005). Reduced striatal DAT levels are seen in unmedicated BD patients (Anand *et al*, 2011) and postmortem tissue (Rao *et al*, 2012). Thus, the relationship between reduced DAT functioning and its contribution to impaired risk-based decision-making in BD patients may be important, but remains undetermined.

Previously, we reported that mice with reduced DAT functioning mimicked abnormal behaviors of BD mania patients (Perry *et al*, 2009). Mice that are hyperdopaminergic via genetic DAT knockdown (KD; Zhuang *et al*, 2001) or pharmacological DAT inhibition (GBR12909 treatment) exhibited this profile. To determine whether reduced DAT functioning could impair decision making under risk, we compared single-session IGT performance of patients with BD and mice with chronic (DAT KD) and acute (GBR12909) reductions of DAT functioning. A single-session IGT was used for consistency with the human IGT and to measure dynamic changes in decision making after rewards or punishments. We predicted that: (1) decision making would be impaired in BD patients; (2) subpopulations of mice would be identifiable in the mouse IGT based on risk learning; and (3) both chronic and acute reductions of DAT functioning would impair IGT performance similar to deficits observed in BD.

MATERIALS AND METHODS

Participants

Sixteen participants (18–55 years old) who met SCID (Structured Clinical Interview for DSM-IV) criteria for BD were recruited from inpatient and outpatient psychiatric clinics located at the University of California San Diego (UCSD) Medical Center. Nine participants met criteria for a current manic episode (Young Mania Rating Scale score $\geqslant 20$) and seven were classified as hypomanic (Young Mania Rating Scale score = 12–15; Tohen *et al*, 2002). The majority of patients were taking mood stabilizers and/or atypical antipsychotics with the most common medication being valproate and lithium or risperidone, respectively. Seventeen healthy control (HC) participants who had never met SCID criteria for any Axis I psychiatric disorder and did not have first-degree relatives with BD were recruited from advertisements in the San Diego community. BD and HC groups were matched for age, gender, education, and ethnicity, and had equivalent premorbid IQ as assessed by the Peabody Picture Vocabulary Test (Dunn and Dunn, 1997; Table 1). Participants were excluded for: (1) current alcohol or substance dependence; (2) a history of neurological conditions, head trauma, or seizures; (3) treatment with electroconvulsive therapy; (4) stroke or myocardial infarction; and (5) a positive result for cocaine, amphetamine, or phencyclidine on a urine toxicology Rapid Drug screen (Pharmatic Inc., San Diego, CA) administered during the test session. All subjects provided written informed consent to the current protocol approved by the UCSD Institutional Review Board known as the Human Research Protections Program.

Human IGT

Participants were administered a computerized version of the IGT where individuals were required to select from four decks of cards (A, B, C, and D; Bechara *et al*, 1994). This IGT is a decision-making measure included in the National

Table 1 Demographic and Clinical Characteristics of BD Patients and HC Subjects

Parameter	HC ($n = 17$)	BD ($n = 16$)	Group differences
Age (years)	33.9 ± 3.0	33.8 ± 2.8	NS
Gender (male/female)	5 M, 12 F	9 M, 7 F	NS
Education (years)	14.8 ± 0.6	13.9 ± 0.6	NS
Ethnicity (% Caucasian)	47%	75%	NS
Peabody Picture Vocabulary Test	104.7 ± 2.7	96.9 ± 4.2	NS
BD age of onset (years)		23.0 ± 1.8	
BD duration of illness (years)		10.1 ± 1.9	
Number of BD hospitalizations		2.7 ± 0.5	
YMRS score	0.9 ± 0.8	22.3 ± 2.3***	BD > HC
HDRS score	0.9 ± 0.4	9.3 ± 1.2***	BD > HC
Medication			
Antipsychotic alone		3	
Mood stabilizer alone		1	
Antipsychotic + mood stabilizer		9	
Other medications		0	
Not medicated		3	

Abbreviations: BD, bipolar disorder; HC, healthy control; HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.
***$p < 0.001$.

Institute on Drug Abuse PhenX Toolkit (http://phenxtoolkit.org- 31 January 2014, Version 5.7) as part of the National Institute on Drug Abuse-endorsed initiative to promote data harmonization across studies. After selecting a card, a theoretical amount of money was displayed on the screen. Decks A or B resulted in high monetary gains, but also high unpredictable penalties (disadvantageous). Decks C and D paid smaller amounts of money but incurred smaller losses (advantageous; Supplementary Table 1). The task included 100 trials and participants were informed that the goal was to avoid losing money and win as much money as possible (Figure 1). Decision making was measured using a net score calculated by subtracting disadvantageous choices (A + B) from the advantageous choices (C + D).

Mice

Male C57BL/6J ($n = 133$), DAT KD ($n = 31$), and wild-type (WT) littermate ($n = 28$) mice were used throughout the experiments. DAT heterozygous breeders backcrossed onto a C57BL/6J background for >10 generations were sent to UCSD from the University of Chicago. All mice were 3–5 months old at the time of testing and weighed between 21 and 34 g. All animals 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 1900 hours, off at 0700 hours). All mice had *ad libitum* access to water and were food-restricted at 85% of their free-feeding weight during the periods of testing (during the dark phase of the day–night cycle between 0800 hours and 1800 hours). All 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.

Drugs

GBR12909 dihydrochloride was purchased from Sigma Aldrich (St Louis, MO, USA) and dissolved in saline after heating (45 °C, 60 min; van Enkhuizen *et al*, 2013a; Young *et al*, 2010). GBR12909 was injected intraperitoneally with a volume of 10 ml/kg, immediately before testing. Free-base drug weight was used in drug calculations.

Mouse IGT

A single-session IGT was developed for mice based on the original task designed by Rivalan *et al* (2009). Sixteen five-hole operant chambers were used for the IGT (Supplementary Methods) to provide four illuminated options consistent with the task in rats. In short, mice had 10 s to holepoke in one of four illuminated holes. Mice were rewarded with strawberry milkshake or punished with a time-out period depending on the reward schedule (Figure 1). Consistent with the original rat task, two options delivered large rewards or long time-out penalties (disadvantageous), whereas the other two options delivered smaller rewards or shorter time-out penalties (advantageous). The reward and punishment probabilities used here were consistent with those of Rivalan *et al* (2009). The high punishment durations used here for mice were lower, however, 66 and 132 s compared with 222 and 444 s because of the punishment sensitivity observed in mice. Even with this reduced duration, advantageous choices correlated most strongly with avoiding punishment as opposed to gaining rewards (Supplementary Figure 8), unlike rats (Rivalan *et al*, 2009). Decision making was measured as *%advantageous choices* and several other measures were recorded and presented (Table 2).

Characterization of the Single-Session Mouse IGT

After stabilization of responding on a simple fixed-ratio schedule (Supplementary Materials and Methods), single-session performance of C57BL/6J mice ($n = 44$) was assessed in the IGT.

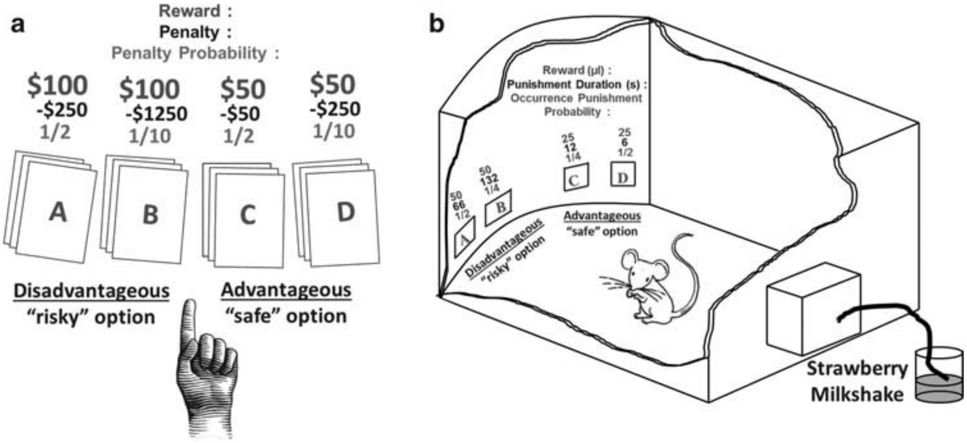

Figure 1 Illustrative comparison between the human Iowa Gambling Task (IGT) and the single-session mouse IGT. (a) Human subjects sequentially selected one card among four available decks for 100 trials and were instructed to try to win as much money as possible. (b) The IGT for mice was developed based on the original work in rats by Rivalan *et al.* After operant training, mice were tested in the single-session 1-h long IGT. After a 5-s delay, the mouse could holepoke among the illuminated holes (A–D) for a 10-s period. For the human and mouse paradigms, the selected card or hole determined the given reward value (money for humans, strawberry milkshake for mice; in red), or punishment value (monetary loss for humans, flashing cue light for mice; in black), according to the associated probability (in blue). Based on preliminary data, lower punishment durations were used for mice compared with rats. In both IGTs, two small reward/low punishment options (C and D) were ultimately advantageous, whereas the other two high reward/high punishment options (A and B) were disadvantageous.

Table 2 Description of the Behavioral Measures Used in the Single-Session Mouse Iowa Gambling Task

Measures	Description
% Advantageous 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
(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
(p) Safe-shift	Probability of choosing disadvantageous options after being punished from advantageous options
(p) Risky-shift	Probability of choosing advantageous options after being punished 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)

Effects of Chronic Reductions of DAT Functioning on IGT Performance

DAT KD ($n = 31$) and WT littermates ($n = 28$) were trained to holepoke. After stabilization of responding, the IGT performance of these mice were assessed and compared.

Effects of Acute Reductions of DAT Functioning on IGT Performance

After stabilization of responding, C57BL/6J mice ($n = 89$) naïve to the IGT received saline ($n = 29$), GBR12909 at 9 ($n = 30$) or 16 mg/kg ($n = 30$; van Enkhuizen *et al*, 2013b; Young *et al*, 2010) and were challenged in the IGT.

Quantifying Individual Differences in Learning Performance

Based on previous observations (Rivalan *et al*, 2009), we examined the performance of individual mice and identified three different subpopulations. The total trials of each group were split into three trial periods based on their total trials completed. These subpopulations were quantified by subtracting % advantageous choices of trial period 1 from % advantageous choices of trial period 3. Good, intermediate, and poor decision makers were stratified as (1) >0.5, (2) between 0.5 and -0.5, and (3) <0.5 standard deviations from the mean, respectively. This stratification was made for each genotype or drug treatment group separately.

Post-Reward/Punishment Decision-Making: Win-Stay/Lose-Shift Strategies

The likelihood of a subject repeatedly choosing a card/stimulus following a reward from the advantageous options (safe-stay) and disadvantageous options (risky-stay) was compared with their likelihood of selecting a different choice following punishment from the advantageous (safe-shift) and disadvantageous options (risky-shift; Supplementary Methods).

Statistical Analyses

Human and mouse choices were analyzed over three equal blocks of trials. Human IGT net score was analyzed using analysis of variance with group (BD, HC) as a between-subject factor and trial block as a within-subject factor. Animal choices were analyzed using analyses of variance with trial period as a within-subject factor, and genotype, drug, and group as between-subject factors. Group was determined by quantification of learning as described above. Subjects with $\leqslant 10$ completed trials per trial period were excluded from analysis. The % advantageous choice preference was compared with chance (50%) using a one-sample *t*-test. Tukey *post hoc* analyses of statistically significant main or interaction effects were performed where applicable and Cohen's *d* effect sizes were calculated. Where appropriate, planned comparison paired *t*-tests were conducted between groups. The α level was set at 0.05. All analyses were performed using SPSS (19.0, Chicago, IL, USA).

RESULTS

Human IGT Performance

There was a significant difference in decision-making ability between HC and BD subjects ($F(1,31) = 6.7$, $p < 0.05$; Figure 2a), indicating that BD subjects made less advantageous choices compared with HC subjects ($p < 0.05$; effect size $[d] = 0.91$). Net score increased significantly over three trial blocks in the HC group ($F(2,32) = 3.5$, $p < 0.05$; Figure 2b) with only a trend in the BD subjects ($F(2,30) = 2.9$, $p = 0.070$). Traditional IGT analyses over five trial blocks indicated that net score increased significantly over time in both the HC ($F(4,64) = 3.3$, $p < 0.05$) and BD subjects ($F(4,60) = 3.1$, $p < 0.05$; Supplementary Figure 1). Interestingly, despite the majority of HC subjects increasing their net score over time, some individuals did not, whereas others decreased advantageous preference over time (Figure 2e).

Win-Stay/Lose-Shift Strategies in BD Subjects

All subjects increased safe-stays over time ($F(2,62) = 5.3$, $p < 0.05$; Supplementary Figure 2A), but the BD subjects tended to make less safe-stays compared with HCs ($F(1,31) = 4.0$, $p = 0.054$; Figure 2c). No significant effects were observed for risky-stays (Supplementary Figure 2B). BD subjects made more safe-shifts compared with HCs ($F(1,31) = 5.0$, $p < 0.05$; Figure 2d), but there were no effects for risky-shifts (Supplementary Figure 2D). Hence, BD

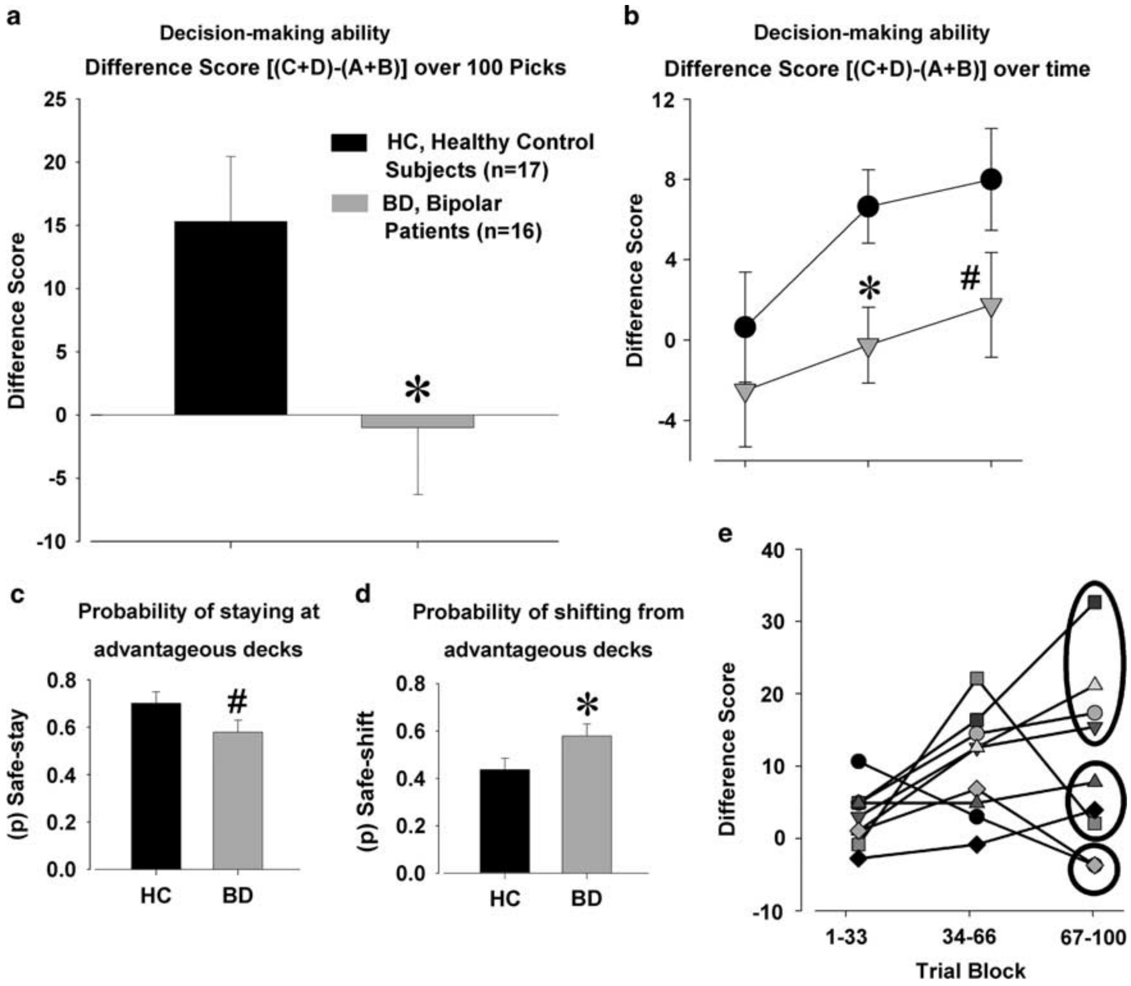

Figure 2 Iowa Gambling Task (IGT) performance of bipolar disorder (BD) and healthy control (HC) subjects. (a) Over 100 card picks, the BD group had a significantly lower net difference score compared with HC subjects. (b) When analyzed over three trial blocks, BD subjects performed poorly compared with HC subjects in blocks two and three. (c) Compared with HC subjects, BD subjects tended to make fewer low-reward safe-stays. (d) Compared with HC subjects, BD subjects switched more often to the high-reward decks directly after losing at the low-reward decks (safe-shifts). (e) Inter-individual differences of a subset of HC subjects ($n = 9$) are displayed, indicating that the majority increases their net score over time, whereas others remain the same or decrease their net score over time. Data are presented as the mean ± SEM, $^{*}p < 0.05$ and $^{\#}p < 0.1$ when compared with HC subjects.

subjects were less likely to stay at the safe low-reward options but as likely to stay at the risky high-reward options.

Inter-Individual Differences of C57BL/6J Mice in a Single-Session IGT

Mice were grouped into good (32%), intermediate (48%), or poor (20%) decision makers based on their IGT learning performance (see Methods).

Advantageous choices. A group × trial period interaction ($F(4,82) = 19.1$, $p < 0.001$; Figure 3a) indicated that good decision makers increased advantageous choices ($F(2,26) = 12.0$, $p < 0.01$), whereas poor decision makers decreased advantageous choices ($F(2,16) = 16.9$, $p < 0.001$) over time.

Other behavioral measures. Independent of group, mice reacted faster over time ($F(2,82) = 4.8$, $p < 0.05$), whereas omissions and premature responses did not differ ($F < 1$, NS) over time (Table 3).

Win-Stay/Lose-Shift Strategies of C57BL/6J Mice

Good decision makers exhibited more safe-stays over time ($F(2,26) = 3.8$, $p < 0.05$; Figure 3b) and compared with poor decision makers at the end of the session ($p < 0.01$). Poor decision makers, however, tended to exhibit more risky-stays over time ($F(2,16) = 3.1$, $p = 0.074$; Supplementary Figure 3A) and compared with good decision makers at the end of the session ($p < 0.05$). Poor decision makers exhibited more safe-shifts compared with good decision makers in trial period 3 ($p < 0.01$; Figure 3c), while they made less risky-shifts over time ($F(2,16) = 5.1$, $p < 0.05$; Supplementary Figure 3B).

IGT Performance of DAT WT and KD Mice

A main group effect ($F(2,53) = 4.4$, $p < 0.05$), trial period × group interaction ($F(4,106) = 30.2$, $p < 0.001$), and trends

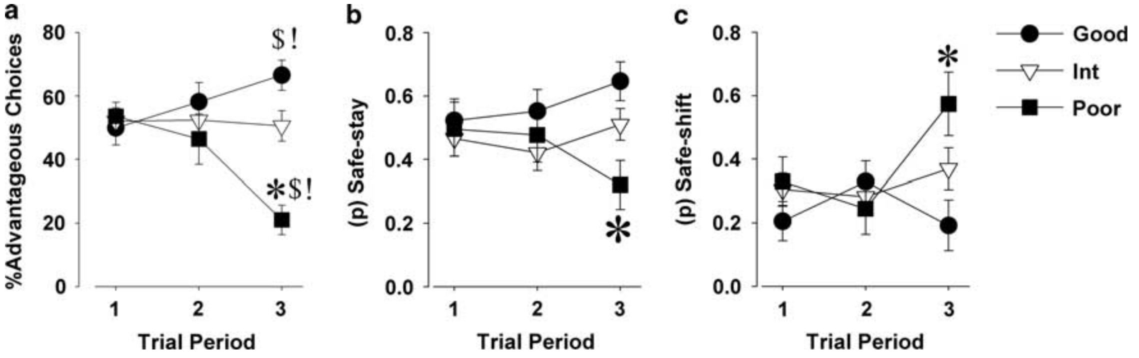

Figure 3 Iowa Gambling Task (IGT) performance of C57BL/6J mice identified as good, intermediate, and poor decision makers. (a) Good decision makers chose advantageous options, whereas poor decision makers preferred disadvantageous options as the session progressed. (b) Good decision makers made more safe-stays over time, and compared with poor decision makers at the end of the session. (c) By the final trial period, poor decision makers made more safe-shifts compared with good decision makers. Data are presented as the mean ± SEM, $^{*}p<0.05$ when compared with good decision makers, $^{\$}p<0.05$ when compared with intermediate decision makers, and $!p<0.05$ when compared with chance.

Table 3 Motivational/Motor Impulsivity Measures of Mice in the Iowa Gambling Task

Measure	Group	C57	WT	KD	Saline	GBR 9	GBR 16
Mean choice latency (s)	Good	2.86 ± 0.24	4.09 ± 0.24	3.37 ± 0.20^{a}	4.31 ± 0.36	3.72 ± 0.30	4.91 ± 0.30
	Interm	3.11 ± 0.20	4.07 ± 0.21	3.11 ± 0.24^{a}	4.88 ± 0.26	4.04 ± 0.32^{a}	4.25 ± 0.27^{b}
	Poor	3.30 ± 0.30	4.70 ± 0.41	3.37 ± 0.34^{a}	4.57 ± 0.42	4.59 ± 0.29	4.45 ± 0.33
Omissions (%)	Good	7.60 ± 3.05	17.21 ± 2.82	6.31 ± 2.30^{a}	18.75 ± 4.31	7.65 ± 3.60^{a}	24.17 ± 3.60
	Interm	10.79 ± 2.49	14.23 ± 1.80	7.62 ± 2.14^{a}	20.72 ± 3.16	17.84 ± 3.80	23.68 ± 3.29
	Poor	14.93 ± 3.80	17.77 ± 2.47	7.26 ± 2.02^{a}	23.84 ± 5.10	21.29 ± 3.44	17.10 ± 4.03
Premature responses	Good	5.21 ± 1.82	18.13 ± 10.83	47.00 ± 8.84^{b}	1.05 ± 1.55	2.23 ± 1.30	2.90 ± 1.30
	Interm	9.10 ± 1.48	17.79 ± 6.01	47.70 ± 7.11^{a}	3.69 ± 1.14	1.52 ± 1.37	3.44 ± 1.19
	Poor	6.67 ± 2.27	10.83 ± 8.63	32.33 ± 7.05^{b}	2.40 ± 1.84	1.42 ± 1.24	4.50 ± 1.45

Abbreviations: Interm, intermediate; KD, knockdown; WT, wild type.
$^{a}p<0.05$.
$^{b}p<0.1$ when compared with WT/saline.

toward trial period × genotype (F(2,106) = 3.1, $p = 0.058$) and trial period × genotype × group interactions (F(4,106) = 2.3, $p = 0.078$) were observed. Similar to C57BL/6J mice, good decision makers increased and poor decision makers decreased advantageous choices over time.

Good decision makers. Both WT and KD mice made increased advantageous choices over time (F(2,36) = 27.6, $p<0.001$). A trial period × genotype interaction (F(2,36) = 5.0, $p<0.05$) indicated that KD mice made significantly less advantageous choices than WT mice during trial period 2 ($p<0.05$; effect size [d] = 1.22; Figure 4a). Importantly, WT mice performed above chance in trial periods 2 and 3 ($p<0.05$), whereas KD mice did not differ from chance. No genotype differences were observed in either the intermediate or poor decision makers (Supplementary Figure 4A and B).

Other behavioral measures. KD mice exhibited fewer omissions (F(1,53) = 24.1, $p<0.001$), increased premature responses (F(1,53) = 15.4, $p<0.001$), and faster reaction times (F(1,53) = 20.7, $p<0.001$) compared with WT mice (Table 3). No group differences or interaction with genotype were observed, neither was there an effect of genotype on total trials completed (F < 1, NS; Supplementary Table 2).

Win-Stay/Lose-Shift Strategies of DAT KD and WT Mice

Although both WT and KD tended to make more safe-stays over time (F(2,106) = 3.0, $p = 0.055$; Figure 4b), a trial period × genotype (F(2,106) = 4.2, $p<0.05$) and trial period × group (F(4,106) = 8.8, $p<0.001$) interaction indicated that among good performing mice, KD mice exhibited less safe-stays than WT mice during trial period 3 ($p<0.01$). No other differences in genotype were observed for any of the measures (Figure 4c, Supplementary Figure 5A and B).

IGT Performance of Mice Treated with the Acute DAT Inhibitor GBR12909

Overall, a trial period × group (F(4,152) = 40.0, $p<0.001$) and trial period × GBR12909 (F(4,152) = 3.2, $p<0.05$) interactions indicated similar overall group differences as above.

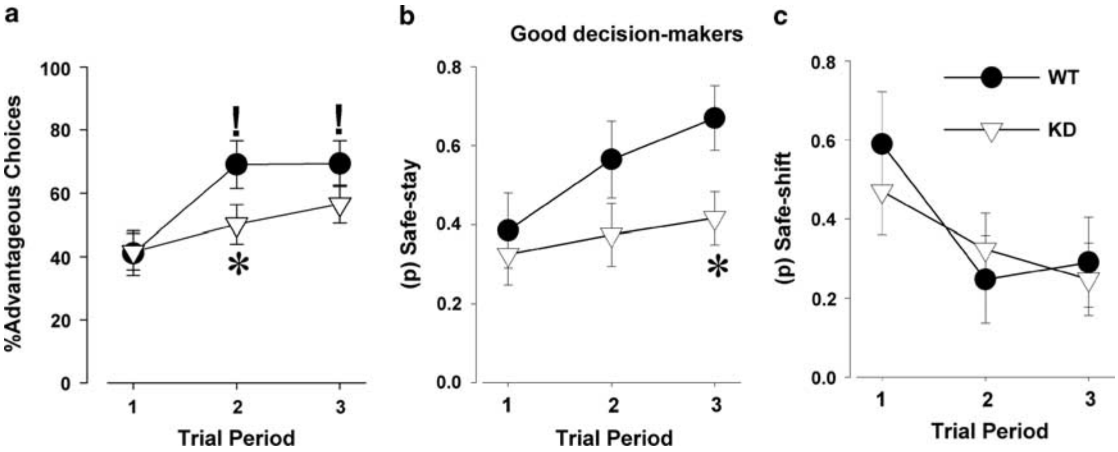

Figure 4 Iowa Gambling Task (IGT) performance of dopamine transporter (DAT) knockdown (KD) and wild-type (WT) littermates identified as good decision makers. (a) WT mice rapidly increased advantageous choices over time, whereas KD mice increased more gradually and performed poorer in trial period 2. (b) Over time, both WT and KD mice made more low-reward safe-stays, although KD mice stayed significantly less compared with WT mice by the final trial period. (c) Over time, both WT and KD mice shifted less from the advantageous options after punishment (safe-shifts). Data are presented as the mean ± SEM, $*p<0.05$ and $^{\#}p<0.1$ when compared with WT, $!p<0.05$ when compared with chance.

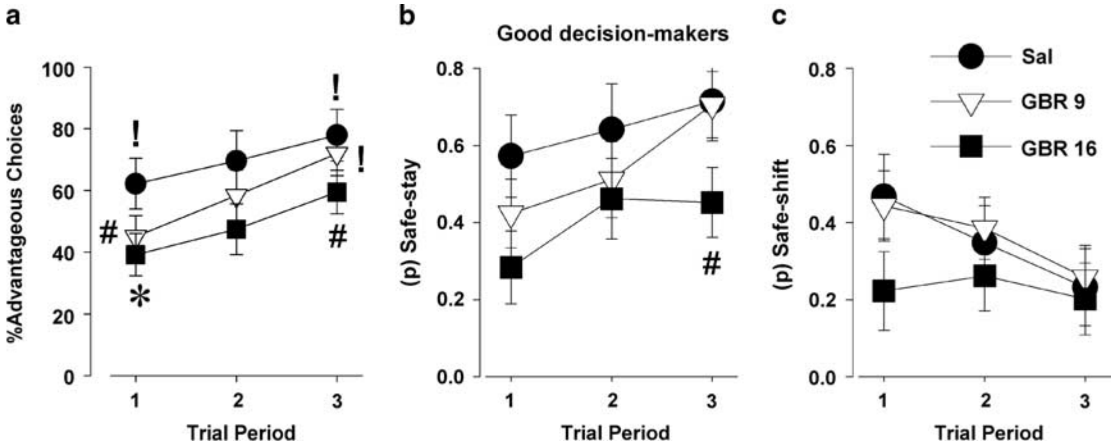

Figure 5 Iowa Gambling Task (IGT) performance of C57BL/6 mice, identified as good decision makers, treated with the acute dopamine transporter (DAT) inhibitor GBR12909. (a) Both saline-treated (Sal) mice and GBR12909-treated (GBR 9 and GBR 16) mice increased advantageous choices over time. However, GBR12909-treated mice exhibited impaired decision making compared with saline-treated mice, especially at 16 mg/kg. (b) Over time, all mice made more low-reward safe-stays, although mice receiving GBR12909 at 16 mg/kg stayed significantly less compared with saline-treated mice. (c) No effect of GBR12909 treatment was observed on the animals' decrease in shifting from the advantageous options after punishment (safe-shifts) over time. Data are presented as the mean ± SEM, $*p<0.05$ and $^{\#}p<0.1$ when compared with saline, $!p<0.05$ when compared with chance.

Good decision makers. Although both saline- and GBR12909-treated mice learned to select advantageous choices over time (F(2,48) = 32.1, $p<0.001$), mice receiving GBR12909 at 16 mg/kg made significantly less advantageous choices than saline-treated mice overall ($p<0.05$; effect size $[d]=0.95$; Figure 5a). Moreover, saline-treated mice performed above chance in trial periods 1 and 3 ($p<0.05$), whereas mice receiving GBR12909 at 16 mg/kg did not differ from chance and mice receiving 9 mg/kg GBR12909 were only above chance in trial period 3 ($p<0.05$). No differences in treatment were observed in both the intermediate and poor decision makers (Supplementary Figure 6A and B). These findings indicate deleterious effects of GBR12909 on risk-based decision-making of mice.

Other behavioral measures. No overall effects of GBR12909, group differences, or interaction were observed, although a main effect of GBR12909 in the good decision makers (F(2,24) = 8.1, $p<0.01$) indicated that mice receiving 9 mg/kg GBR12909 exhibited fewer omissions compared with saline-treated mice ($p<0.05$; Table 3). There was no effect of GBR12909 on total trials completed (F = 1.3, NS; Supplementary Table 2).

Win-Stay/Lose-Shift Strategies of GBR12909-Treated Mice

Although all good decision makers made more safe-stays over time (F(2,46) = 8.6, $p<0.01$), mice receiving GBR12909 at 16 mg/kg exhibited less safe-stays than saline-treated mice overall ($p < 0.05$; Figure 5b). Except for mice treated with 9 mg/kg GBR12909 making more risky-stays compared with saline-treated mice initially (Supplementary Figure 7A), no other differences were observed for any other measures (Figure 5c, Supplementary Figure 7B).

DISCUSSION

Impaired IGT performance was observed in BD patients compared with healthy subjects. In the single-session IGT task for mice, we demonstrated that dynamic decision making could be assessed when the animals were exposed to risk and reward contingencies similar to those in the human IGT. Stable subgroups were identified among mice, consistent with rats (Rivalan *et al*, 2009) and inter-individual differences in humans (Weller *et al*, 2010; illustrated in Figure 2e). Importantly, good decision makers increased safe-stays and decreased risky-stays over time, a pattern consistent with human IGT studies (Bechara *et al*, 2002b). As hypothesized, both chronic and acute reduced DAT functioning via genetic KD and GBR12909, respectively, deleteriously affected IGT performance in good decision makers. In mice, as in BD patients, this deficit was driven by a reduced likelihood to maintain responding for low rewards, without a difference for high rewards. Hence, the impaired decision-making profile of these mice was consistent with that of BD patients (Adida *et al*, 2011; Ibanez *et al*, 2012).

The IGT performance deficits of BD patients are consistent with previous studies (Adida *et al*, 2008; Clark *et al*, 2001; Yechiam *et al*, 2008), with deficits observed across several phases of BD (euthymia, depression, and mania; Adida *et al*, 2011). We provided novel analyses to investigate the underpinnings of this deficit. Manic BD patients studied here tended to pick less from the safe decks repeatedly (less safe-stays) and were more likely to switch to the risky decks after punishment (more safe-shifts). Such attendance to gains rather than loss are also seen in BD euthymic patients administered the DA D_2/D_3 receptor agonist pramipexole (Burdick *et al*, 2014). In rats, DA D_1 and D_2 receptor contributions to win-stay/lose-shift strategies have been assessed during reward unpredictability (St Onge *et al*, 2011). The lack of punishment or varied reward levels in this reward probability task limits direct comparison to these data, but highlights how this mouse IGT paradigm can be used to examine the neural contribution to such reduced safe-stays and increased safe-shifts. Understanding differences in punishment- and reward-related learning is critical given that depressed subjects make punishment-sensitive decisions in the IGT (Adida *et al*, 2011), whereas substance-dependent (Bechara *et al*, 2002b) and remitted BD subjects (Brambilla *et al*, 2012) attend to high rewards irrespective of risk.

This preference for high reward of BD patients and the development of the single-session mouse IGT enabled our primary investigation, determining whether this pattern is recapitulated in hyperdopaminergic mice because of reduced functional DAT levels. We observed that among regular C57BL/6J mice, some mice developed a preference for low-reward advantageous options ('good decision makers'). In contrast, other mice developed a bias for high-reward disadvantageous options ('poor decision makers'), whereas a third group of mice did not develop a response preference ('intermediate decision makers'). Such inter-individual differences have been observed in rat (Rivalan *et al*, 2009) and human IGT studies (Figure 2e), reflecting underlying risk-prone traits. Greater proportions of humans exhibit preference for advantageous choices (Bechara and Damasio, 2002a; Weller *et al*, 2010). The high number of poor or intermediate decision-making mice may represent too many risk-prone animals masking any genotypic or pharmacological effects, hence these differences were observed only in good decision makers. Despite subgroup differences in decision making over time, these groups did not differ on secondary measures of omissions, premature responses, and reaction times. This dissociation emphasizes the selectivity of risk-learning performance suggesting that it is unrelated to motor impulsivity or motivational features. Together, these data support the use of the single-session rodent IGT to examine risk-based decision making and highlight the importance of inter-individual differences in risk preference.

Both chronic and acute reductions of functional DAT in mice negatively affected risky decision making. Within the good decision makers, KD mice exhibited impaired decision making compared with WT mice, similar to impaired IGT performance of BD patients compared with HCs. Similar risk preference of KD mice has been observed before in a multiple session rodent IGTs (Young *et al*, 2011), but importantly the present study utilizes a single-session IGT, consistent with the human IGT. Because of the similarity between tasks, we could analyze dynamic decision making after rewards or punishment as was conducted in humans. Poorer KD performance was likely mediated by their sensitivity to high reward, reflected by less likelihood of staying with low-reward options. The effects of acute DAT inhibition via GBR12909 treatment on decision making were similar to performance in KD mice. GBR12909 (16 mg/kg) significantly increased risk preference compared with saline driven by reduced tendency to stay at low rewards. Supporting these effects, we previously observed that GBR12909 modestly increased risk preference in a multiple session mouse IGT (van Enkhuizen *et al*, 2013b). Utilizing the same multiple session tasks in rats, however, simultaneous administration of GBR12909 and the norepinephrine transporter (NET) inhibitor atomoxetine was required in order to disrupt decision making (Baarendse *et al*, 2013). This disparity in results may reflect task differences or species differences because potencies of DAT and NET inhibitors vary between rats compared with mice and humans (Han and Gu, 2006; Rothman and Baumann, 2003). In humans, limited pharmacological IGT studies have been performed, although reduced DA activity impaired decision making in one study (Sevy *et al*, 2006). Interestingly, treatment with modafinil (an atypical stimulant with DAT inhibition properties) also impaired decision making in low pathological gamblers in the IGT (Zack and Poulos, 2009). Overall, the findings of reduced DAT functioning in mice are consistent with BD patients making less repeated picks from low-reward decks.

The importance of our findings is highlighted from studies indicating that polymorphisms in the *DAT* gene may induce lower DAT levels in patients with BD (Anand *et al*, 2011; Pinsonneault *et al*, 2011). Lower striatal DAT levels have also been observed in people with ADHD (Fusar-Poli *et al*, 2012) and seasonal affective disorder (Neumeister *et al*, 2001). People with ADHD also exhibit increased risky choices in the IGT (Mantyla *et al*, 2012), albeit to a lesser extent when compared with BD (Ibanez *et al*, 2012). Although impaired decision making of the reduced DAT model animals here could therefore resemble other clinical populations, the consistencies of BD patient IGT performance including the sensitivity for rewards, to our reduced DAT functioning in mice are striking. These findings are reinforced by previous observations of parallels between behavior of these DAT models and that of BD patients in other paradigms (Henry *et al*, 2013; Perry *et al*, 2009; van Enkhuizen *et al*, 2012). Moreover, supporting the increased reward-seeking trait of DAT KD mice, chronic DAT reduction also resulted in faster reaction times, fewer omissions, and increased premature responses in both the present and previous studies (Young *et al*, 2011). Similarly, and as observed previously (van Enkhuizen *et al*, 2013b), GBR12909 at 9 mg/kg reduced omissions, although no significant effects were found on motor impulsivity in contrast to the increased motor impulsivity with this dose that has been observed repeatedly in mice (Loos *et al*, 2010; van Enkhuizen *et al*, 2013b) and rats (Baarendse *et al*, 2013). Indeed, increased motivation and motor impulsivity of both DAT KD and to a lesser degree GBR12909-treated mice may be interpreted as consistent with the exaggerated hedonia-like symptomatology observed in BD (Cassidy *et al*, 1998). Therefore, both DAT model animals resemble patients with BD in both behavior and putative etiology.

The differences on motivational and impulsivity measures seen between the chronic and acute DAT inhibition models may not be surprising. Previously, acute DAT blockade with GBR12909 did not affect reaction-times in mice (Loos *et al*, 2010; van Enkhuizen *et al*, 2013b). In contrast, constitutive DAT KD mice may have altered neurotransmission besides hyperdopaminergia (eg, DAT KD mice exhibit reduced choline transporter expression; Parikh *et al*, 2006), putatively contributing to these behavioral differences. Developmental changes resulting from reduced DAT expression may reproduce altered receptor levels in patients with BD. Hence, chronic reductions of DAT expression in mice may model more aspects of BD than acute DAT inhibition alone. The etiological validity of the chronic DAT KD model is likely limited, however, by the fact that these animals express only 10% of the transporter (Zhuang *et al*, 2001), whereas only a ~20% reduction of DAT availability is observed in euthymic BD patients (Anand *et al*, 2011). As yet, DAT levels in BD patients in the manic phase have yet to be established.

A limitation of the current study is the lack of DAT expression levels of our BD subjects performing the IGT. Hence, although we predicted increased risk-taking in mice with reduced DAT expression because of the reduced expression observed in unmedicated patients, it will be important for future studies to combine these behavioral assessments with physiological measurements, eg, via PET (Anand *et al*, 2011) or measurement in peripheral lymphocytes (Buttarelli *et al*, 2011). Another limitation is that experimental animals are kept in stable and controlled environments (ie, circadian rhythms/light exposure), whereas evidence suggests that environmental factors such as long day-lengths contribute to BD symptoms (Blumberg, 2012). Interestingly, long activity day-lengths may further induce a hyperdopaminergic state (Dulcis *et al*, 2013), which theoretically could exacerbate the reduced DAT levels of BD patients. Future tests will therefore include mice with ~40–50% expression of the DAT and concurrent environmental manipulations such as aberrant light exposure to assess the relevance of these manipulations in modeling BD or other potentially DAT-mediated disorders such as ADHD. Cross-species translational studies can further help elucidate the differences in decision making and other measures between individuals with ADHD and BD. Examining a selective NET blocker may prove useful, given its role in the treatment of ADHD and previous implication in ameliorating prepulse inhibition deficits in DAT knockout mice (Arime *et al*, 2012; Yamashita *et al*, 2006). Future studies in humans and other model animals for BD (Einat, 2007; Roybal *et al*, 2007) will help delineate the mechanism(s) underlying impaired decision making and contribute to developing therapeutics aimed to treat these deficits.

In summary, BD patients exhibit impaired decision making in the IGT. Using post-reward/punishment decision-making measurements developed from animal studies, we identified evidence to support a high-reward sensitivity in these patients. The development of a dynamic single-session mouse IGT, wherein mice increase advantageous choices over time and post-reward/punishment measurements can be examined aids our translational work. Chronic and acute reductions of DAT functioning in mice deleteriously impacted risk-based decision-making, making mice sensitive to high rewards and mimicking deficits of BD patients. DAT reductions may therefore contribute to poor decision making under risk in BD patients. Finally, the single-session IGT may be used to assess decision-making deficits in other animal models of psychiatric disorders and test putative treatments.

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