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Increased motor impulsivity in a rat gambling task during chronic ropinirole treatment: potentiation by win-paired audiovisual cues

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Abstract

Rationale Chronic administration of $D_{2/3}$ receptor agonists ropinirole or pramipexole can increase the choice of uncertain rewards in rats, theoretically approximating iatrogenic gambling disorder (iGD).

Objectives We aimed to assess the effect of chronic ropinirole in animal models that attempt to capture critical aspects of commercial gambling, including the risk of losing rather than failing to gain, and the use of win-paired sensory stimuli heavily featured in electronic gambling machines (EGMs).

Methods Male Long–Evans rats learned the rat gambling task (rGT; $n = 24$), in which animals sample between four options that differ in the magnitude and probability of rewards and time-out punishments. In the cued rGT ($n = 40$), reward-concurrent audiovisual cues were added that scaled in complexity with win size. Rats were then implanted with an osmotic pump delivering ropinirole (5 mg/kg/day) or saline for 28 days.

Results Chronic ropinirole did not unequivocally increase preference for more uncertain outcomes in either the cued or uncued rGT. Ropinirole transiently increased premature responses, a measure of motor impulsivity, and this change was larger and more long-lasting in the cued task.

Conclusions These data suggest that explicitly signaling loss prevents the increase in preference for uncertain rewards caused by $D_{2/3}$ receptor agonists observed previously. The ability of win-paired cues to amplify ropinirole-induced increases in motor impulsivity may explain why compulsive use of EGMs is particularly common in iGD. These data offer valuable insight into the cognitive-behavioral mechanisms through which chronic dopamine agonist treatments may induce iGD and related impulse control disorders.

Keywords Iowa gambling task · Impulsivity · Risky choice · Decision-making · Gambling disorder · Dopamine agonist

Melanie Tremblay and Michael M. Barrus contributed equally to this work.

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Introduction

Dopamine replacement therapies, used in the treatment of Parkinson's disease (PD) and other movement disorders, are associated with the development of impulse control and addiction disorders, including gambling disorder (GD), hoarding, hypersexuality, and kleptomania, in a subgroup of patients (e.g., Weintraub 2009; Weintraub and Nirenberg 2013). It is difficult to definitively determine from clinical data whether the underlying pathology involved in the original movement disorder is critical for the occurrence of these unwelcome side effects or if individual differences in behavioral traits such as impulsivity or risky decision-making are significant contributing factors (Dagher and Robbins 2009; Voon et al. 2007; Voon et al. 2011a; b). To try and address these critical questions, researchers have evaluated the effects of chronic dopamine agonist treatment in a variety of rodent cognitive-behavioral tests of impulsivity, compulsivity, and risky choice (Cocker et al. 2017; Holtz et al. 2016; Madden

et al. 2010; Rokosik and Napier 2012; Schepisi et al. 2013). The overwhelming conclusion from research performed to date is that the drug treatment itself is largely to blame, independent of damage to the nigrostriatal dopamine system, as in a model of early PD, or baseline preference for uncertain outcomes. However, in order to maximize the translational relevance of these findings, it is important to consider whether they capture all the relevant aspects of the human experience.

With regard to relevance for iatrogenic gambling disorder (iGD), one key feature of commercial gambling is that a failed bet results in the loss of the amount wagered, rather than simply failure to gain (Winstanley and Clark 2016). Given that most rodent behavioral tasks are reinforced with nutritive rewards that are immediately consumed, it has been challenging to model this aspect of gambling in preclinical studies. Nevertheless, a number of such gambling-like paradigms have been developed, which signal loss through either the addition of a bitter substance to the sugar pellet rewards (van den Bos et al. 2006), the concurrent delivery of electric shocks with reward (Simon et al. 2009), or the delivery of punitive time-out periods on unrewarded trials that eat into the amount of time animals have to earn reinforcement (Rivalan et al. 2009; Zeeb et al. 2009). As summarized recently, extant data demonstrate that the addition of a loss component to decision-making paradigms alters the neurobiological basis of the choice process (Winstanley and Floresco 2016). However, to our knowledge, the effects of chronic dopamine agonist treatment have not been determined on such tasks, despite their greater face validity for modeling gambling processes.

The response to reward-paired cues is also thought to play a central role in both the pathology of drug addiction and in the transition from recreational to disordered gambling (Grant and Bowling 2015; O'Brien et al. 1992; van Holst et al. 2012). Cues which predict rewards increase the release of dopamine (Schultz 1998), and repeated exposure to stimuli that predict uncertain outcomes can sensitize the dopamine system (Singer et al. 2012; Zack et al. 2014). Audiovisual cues are used extensively in electronic gambling machines (EGMs) to signal winning outcomes, yet although problematic engagement with such EGMs may represent one of the most addictive types of gambling (Breen and Zimmerman 2002; Chooliz 2010), the impact of such cues on the cognitive response to dopamine replacement therapies has yet to be reported.

Pairing reward delivery in a rat gambling task (rGT) with salient audiovisual cues that increase in complexity with the size of the win increases risky choice through a dopamine D₃ receptor-dependent mechanism (Barrus and Winstanley 2016). During the rGT, rats try and maximize sugar pellets earned through sampling between four different options, signaled by illumination of four response apertures, that differ in size and probability of both potential rewards and time-out punishments (Zeeb et al. 2009). Premature responses made at the response apertures before the lights are illuminated provide an index of motor impulsivity similar to that obtained from the five-choice

serial reaction time task (5CSRT) (Carli et al. 1983) and which can predict self-administration of psychostimulants in an addiction-like manner (Belin et al. 2008; Dalley et al. 2007). Similar to the Iowa gambling task used clinically, selection of options associated with higher potential per-trial gains on the rGT can instead result in disproportionately heavy penalties. Such a choice preference results in less reward per session, is considered risky and maladaptive, and is correlated at the population level with high motor impulsivity (Barrus et al. 2015). Decision-making on the rGT is therefore sensitive to both the presence of reward-paired cues, penalty events designed to approximate losses, and acute challenge with dopaminergic drugs. We therefore hypothesized that chronic treatment with the dopamine D₂ family agonist ropinirole would alter engagement with the task in a manner consistent with iGD or impulse control disorders.

Methods and materials

Subjects

Male Long–Evans rats ($n = 64$; initial weight 250–275 g; Charles River Laboratories, St. Constant, QC, Canada) were pair-housed in a climate-controlled colony room on a reverse 12-h light–dark cycle (lights off 08:00; temperature 21 °C). Rats were food-restricted to 85% of their free feeding weight and maintained on 14 g of standard rat chow, plus the sugar pellets earned in the task (~5 g per day). Water was available ad libitum. Behavioral testing began 1 week following the start of food restriction. All housing conditions and testing procedures were in accordance with the guidelines of the Canadian Council on Animal Care, and all protocols were approved by the Animal Care Committee of the University of British Columbia.

The rGT

Behavioral testing took place in 16 standard five-hole operant conditioning chambers, each enclosed within a ventilated sound-attenuating cabinet (Med Associates Inc., St. Albans, VT, USA), configured as per previous reports (Cocker et al. 2012; Zeeb et al. 2009). Subjects were trained to perform the “standard” uncued rGT ($n = 24$) or the cued rGT ($n = 40$) as described previously (Fig. 1; Adams et al. 2017a; Zeeb et al. 2009, 2013; Zeeb and Winstanley 2011, 2013). Each session lasted 30 min. In brief, subjects chose between four illuminated response apertures, each of which was associated with a different reinforcement schedule, with the two-pellet choice (P2) being optimal in terms of reward earned per unit time. Consistent choice of P1 resulted in more frequent but smaller rewards, whereas options paired with larger reward (P3, P4) ultimately resulted in less reward due to the longer punishing

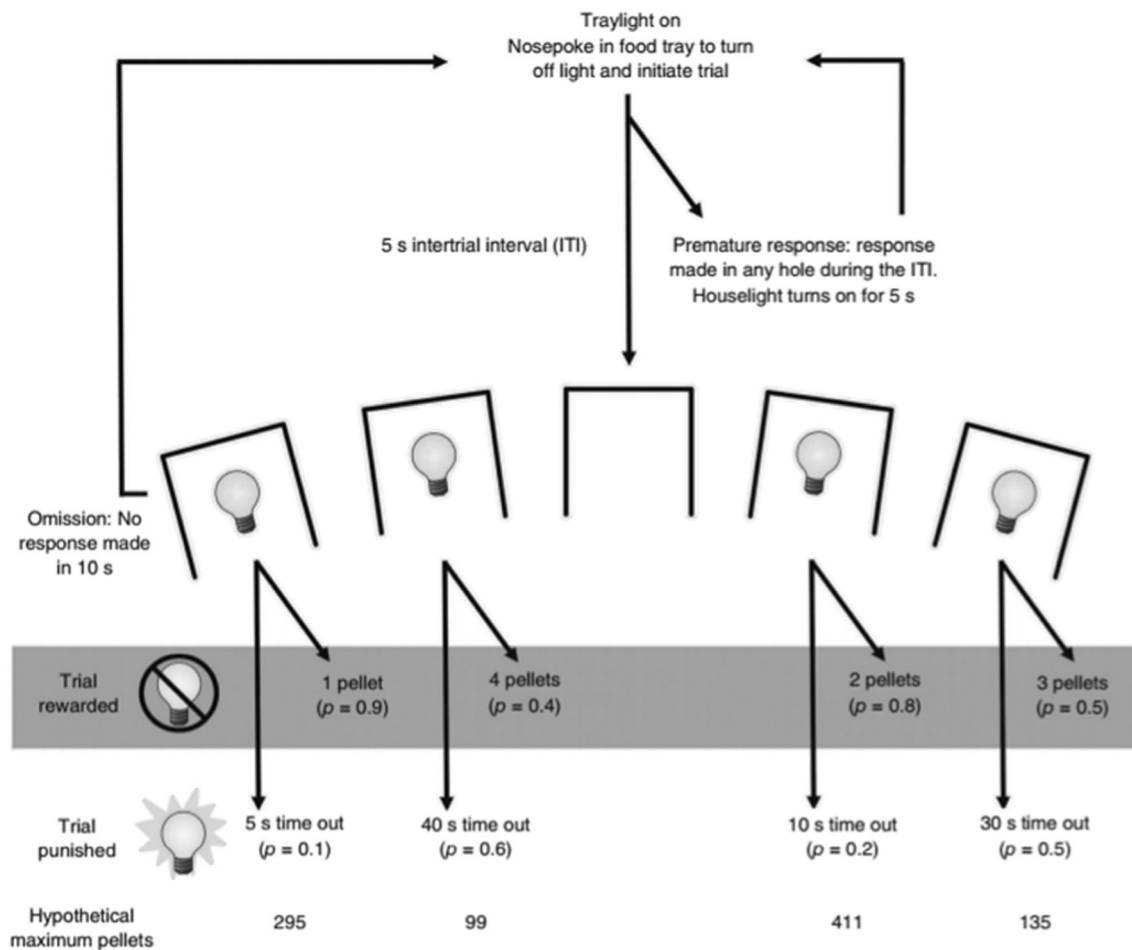


Fig. 1 Task schematic of the rodent gambling task (rGT). Each trial began with the illumination of the tray light. A nosepoke in the tray extinguished the tray light and initiated a 5-s intertrial interval (ITI), during which all lights in the chamber were off. After the ITI, stimulus lights were illuminated in apertures 1, 2, 4, and 5, each of which was associated with a different schedule of reward/punishment. If the animal nosepoked one of the apertures within 10 s, the animal was rewarded or punished according to the schedule associated with that aperture. The size of the reward and the duration of punishment for each option are indicated on the schematic; the p value in brackets beneath each of those indicates the probability of a win or loss on any given trial. On a rewarded trial, the tray light was illuminated and the requisite pellets were dispensed. A

time-outs that occurred on nonrewarded trials. The location of the pellet choice options (P1–4) was counterbalanced across animals. Similar to the 5CSRT, responses made at the array during the 5-s intertrial interval (ITI) that occurred between initiation of the trial and illumination of the response apertures were scored as premature responses and punished by a 5-s time-out period signaled by illumination of the house light. These premature responses provide a concurrent measure of motor impulsivity distinct from risky decision-making.

The structure of the cued rGT was identical to that of the uncued rGT, except that audiovisual cues accompanied reward delivery. Comparable to the experience of human gambling games, the complexity and salience of win-associated

response at the tray then initiated a new trial. On a punished trial, the light in the chosen aperture flashed at a frequency of 0.5 Hz for the duration of the time-out period; all other lights were extinguished. At the end of the time-out, the tray light was once again illuminated and the animal could initiate a new trial. A nosepoke at an aperture during the ITI was scored as a premature response and initiated a 5-s time-out period during which the house light was illuminated. Failure to make a response at an aperture within 10 s of the stimulus lights being illuminated was scored as an omission; the stimulus lights were extinguished, the tray light was once again illuminated, and the animal was able to initiate a new trial. Adapted with permission from Zeeb et al. (2009)

cues increased with the win size, as shown in Table 1. Animals received five daily testing sessions per week until statistically stable patterns of choice behavior were observed over three sessions (51–76 sessions).

Osmotic pump implantation

In each of the cued and uncued rGT experiments, rats were divided into two equivalent groups matched for baseline performance and assigned to receive either 5 mg/kg/day of ropinirole hydrochloride (rGT: $n = 12$; cued rGT: $n = 20$) or 0.9% saline solution (rGT: $n = 12$; cued rGT: $n = 20$) for 28 days. As described previously, the drug was delivered via

Table 1 Stimuli used in the cued rGT

Option	Cue duration (s)	Auditory cues	Visual cues	Variable?
P1	2	1 tone	Flash H1; 2.5 Hz; 2 s	No
P2	2	2 tones, in sequence, 1 s each	Flash H4; 2.5 Hz; 2 s	No
P3	2	3 tones, in sequence, 0.2 s each	Flash H5; 5 Hz; 1 s Flash H2, H3, H4; 5 Hz; 1 s	Yes, 2 patterns
P4	2	6 tones, in sequence, 0.2 s each	Flash H2; 5 Hz; 1 s Flash H1, H2, H3, H4, H5; 5 Hz; 1 s	Yes, 4 patterns

osmotic minipumps (#2ML4, Alzet, DURECT Corporation, Cupertino, CA) implanted subcutaneously using standard surgical techniques (Cocker et al. 2017; Tremblay et al. 2017). At the end of the 28-day period, rats were humanely euthanized by live decapitation.

Data analysis

Analyses were conducted using SPSS (version 22, SPSS/IBM, Chicago, USA). Data from baseline and from 4 weeks of post-operative testing were analyzed in weekly bins of five daily sessions. Analyses in the cued rGT were identical to those performed in the standard version of the task. Data were subjected to a within-subjects repeated-measure analysis of variance (ANOVA) with session (five levels, sessions 1–5) as a within-subjects factor and drug treatment (two levels, ropinirole vs saline) as a between-subjects factor. In both the cued and uncued rGT, the key dependent variable was the percent choice of each option, analyzed as a within-subjects factor (option: four levels, P1–4). Animals were classified as risk-preferring or optimal decision-makers based on their net preference for the advantageous options as measured by a score variable $[(P1 + P2) - (P3 + P4)]$, such that those with a positive score were classified as optimal decision-makers, whereas those with a negative score are deemed risk-preferring (Adams et al. 2017c; Ferland and Winstanley 2016). This distinction was used as a between-subjects factor (choice strategy, two levels). Individual response to the drug was determined using five sessions for each rat with timing and option as within-subject factors (timing: two levels, predrug treatment vs drug treatment; option: four levels, P1–4). A regression analysis was also performed in order to determine if advantageous or disadvantageous choice behavior on the cued/uncued rGT could predict any increase in premature responses following chronic ropinirole. The following variables for nonchoice behavior were also analyzed: percent premature responses, choice latency, collection latency, omissions, and trials completed. As per our previous publications, an arcsine transformation was performed prior to statistical analysis of variables expressed as a percentage in order to limit the effect of an artificially imposed ceiling. The significance level for all effects was $p \leq 0.05$. Violation of the sphericity assumption revealed with

Mauchly's test was corrected using the Greenhouse–Geisser procedure.

Results

The uncued rGT

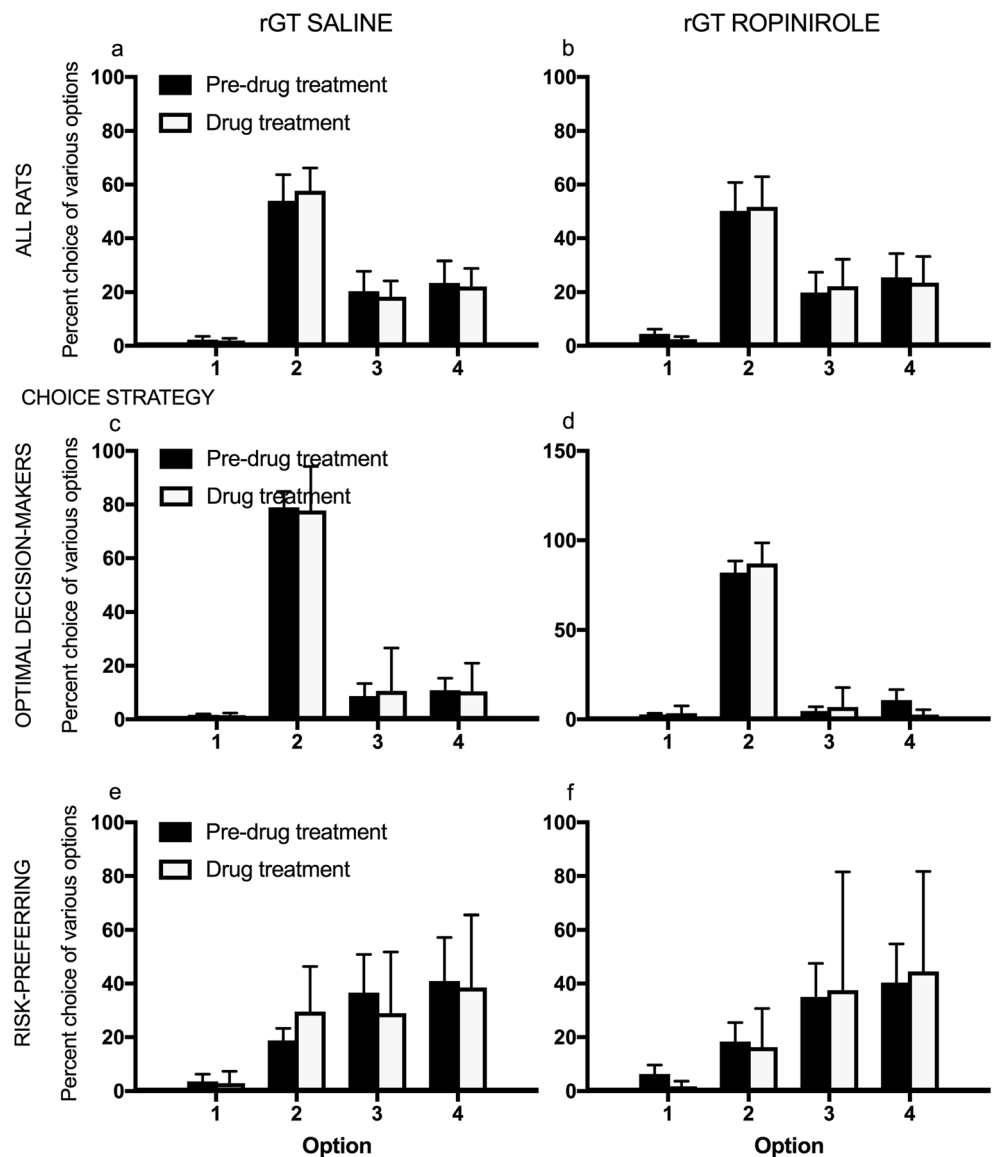
Choice behavior As a group, rats performing the uncued rGT adopted the best strategy on average. However, individual differences in preference for the various options at baseline led to the classification of rats as having adopted either a risk-preferring ($n = 11$) or optimal ($n = 13$) decision-making strategy (option: $F_{3, 66} = 20.74$, $p < 0.001$; option \times choice strategy: $F_{3, 66} = 20.84$, $p < 0.001$).

Chronic ropinirole did not affect the choice of the different options on the rGT at any time point, independent of baseline choice strategy (Fig. 2a, b; Table 2; drug treatment, option \times drug treatment, choice strategy \times drug treatment: all $F_s < 3.18$, all $p_s > 0.090$, NS). There was also no effect of ropinirole on decision-making when comparing any particular week of ropinirole treatment to baseline behavior (drug treatment—weeks 1–4 vs baseline: drug treatment group \times time point: all $F_s < 3.99$, all $p_s > 0.060$, NS).

Nonchoice variables Ropinirole significantly increased the number of premature responses made during the first week of administration, regardless of the rats' baseline preference for the various options, but this effect was no longer evident subsequently (Fig. 3a, b; drug treatment—week 1: $F_{1, 20} = 4.70$, $p = 0.042$; all other weeks: $F_s < 2.67$, all $p_s > 0.118$, NS; Fig. 3c–f; drug treatment \times choice strategy: all $F_s < 0.81$, all $p_s > 0.379$, NS). Choice preference for the advantageous or disadvantageous options at baseline did not predict the increase in premature responses following chronic ropinirole ($F_{1, 10} = 0.97$, $p = 0.348$, $R^2 = 0.088$, NS).

Data values for all other nonchoice variables are given in Table 3. Ropinirole decreased omissions during weeks 2 and 3 of drug administration, independent of rats' decision-making strategy, but again this effect had dissipated by week 4 (drug treatment—week 2: $F_{1, 20} = 6.26$, $p = 0.021$; week 3: $F_{1, 20} = 7.41$, $p = 0.013$; week 4: $F_{1, 20} = 2.51$, $p = 0.129$, NS; drug

Fig. 2 Choice behavior on the uncued rGT during chronic ropinirole. Chronic ropinirole did not alter choice strategy on the uncued rGT. Data is shown predrug treatment and during drug treatment. Percent choice of the various options in the saline- (a) and ropinirole-treated animals (b). Percent choice of the various options in optimal decision-makers (c, d) and in risk-preferring rats (e, f). Data shown are mean \pm SEM



treatment \times choice strategy: all $F_s < 0.50$, all $p_s > 0.488$, NS). At baseline, risk-preferring rats were faster to collect reward, an effect that remained unchanged for the duration of drug treatment (choice strategy: $F_{1, 20} = 16.74$, $p = 0.001$; all other: $F_s > 10.58$, $p_s < 0.004$). Optimal decision-makers also consistently performed more trials, likely due to the more frequent occurrence of longer punishments arising from risk-preferring rats' preference for the disadvantageous options (baseline choice strategy: $F_{1, 20} = 32.46$, $p < 0.001$; all other: $F_s > 20.22$, $p_s < 0.001$). However, ropinirole treatment did not alter the number of trials performed or the latency to choose an option (drug treatment: all $F_s < 3.97$, all $p_s > 0.060$, NS; drug treatment \times choice strategy: all $F_s < 1.47$, all $p_s > 0.239$, NS). Other than reward collection latency and trials completed, there were no other differences between risk-preferring and optimal decision-makers (premature responses, choice latency, omission; choice strategy: all $F_s < 4.25$, all $p_s > 0.051$).

The cued rGT

Choice behavior Similar to previous data using this task (Barrus and Winstanley 2016), a high proportion of rats performing the cued rGT adopted a risky decision-making strategy (risk-preferring: $n = 30$; optimal decision-makers: $n = 10$; option: $F_{3, 114} = 15.64$, $p < 0.001$; option \times choice strategy: $F_{3, 114} = 21.07$, $p < 0.001$).

We found a main effect of chronic ropinirole on choice in the first week of treatment, but this was not associated with a specific increase or decrease in the choice of any of the options in particular and was not evident in subsequent weeks (Fig. 4a, b; Table 4; week 1—drug treatment: $F_{1, 36} = 5.13$, $p = 0.030$; option \times drug treatment: $F_{3, 108} = 0.93$, $p = 0.431$, NS; Fig. 4c–f; drug treatment \times choice strategy: $F_{1, 36} = 0.51$, $p = 0.478$, NS; weeks 2–4—drug treatment: all $F_s < 2.22$, all $p_s > 0.145$, NS). This effect was also evident when the first

Table 2 Choice behavior on the rGT during chronic ropinirole

	Option	Time point				
		Predrug treatment	Week 1	Week 2	Week 3	Week 4
Saline Risk-preferring	P1	3.60 ± 2.65	3.74 ± 2.73	4.79 ± 2.57	3.13 ± 2.42	2.95 ± 1.93
	P2	18.82 ± 4.48	18.40 ± 5.77	27.73 ± 8.50	22.65 ± 6.66	29.57 ± 7.53
	P3	36.60 ± 14.31	32.46 ± 12.66	27.78 ± 10.47	30.53 ± 10.49	28.96 ± 10.21
	P4	40.99 ± 16.21	45.40 ± 17.66	39.69 ± 14.00	43.70 ± 15.10	38.52 ± 12.09
Saline Optimal decision-makers	P1	1.37 ± 0.70	1.56 ± 0.58	1.25 ± 0.55	1.38 ± 0.58	1.12 ± 0.47
	P2	78.99 ± 5.87	78.27 ± 6.04	75.23 ± 7.48	76.78 ± 7.70	77.78 ± 6.22
	P3	8.74 ± 4.65	8.34 ± 5.31	12.03 ± 7.85	11.25 ± 8.02	10.63 ± 6.06
	P4	10.90 ± 4.51	11.83 ± 4.50	11.49 ± 4.34	10.59 ± 3.86	10.47 ± 3.96
Ropinirole Risk-preferring	P1	6.25 ± 3.35	5.09 ± 2.37	2.16 ± 0.93	2.09 ± 0.93	1.57 ± 0.88
	P2	18.40 ± 7.06	19.88 ± 6.70	16.01 ± 6.50	16.42 ± 5.37	16.32 ± 5.87
	P3	35.00 ± 12.53	31.58 ± 11.51	37.60 ± 15.43	38.95 ± 16.95	37.56 ± 17.96
	P4	40.34 ± 14.48	43.46 ± 14.33	44.23 ± 15.86	42.54 ± 14.90	44.55 ± 15.18
Ropinirole Optimal decision-makers	P1	2.63 ± 0.80	5.64 ± 2.86	6.74 ± 3.38	5.46 ± 2.49	3.40 ± 1.68
	P2	81.96 ± 6.50	76.92 ± 6.77	79.76 ± 6.78	84.19 ± 4.85	87.09 ± 4.70
	P3	4.66 ± 2.45	9.16 ± 4.10	5.80 ± 2.67	6.36 ± 3.26	6.91 ± 4.48
	P4	10.75 ± 5.95	8.28 ± 4.21	7.71 ± 4.65	3.98 ± 1.70	2.60 ± 1.17

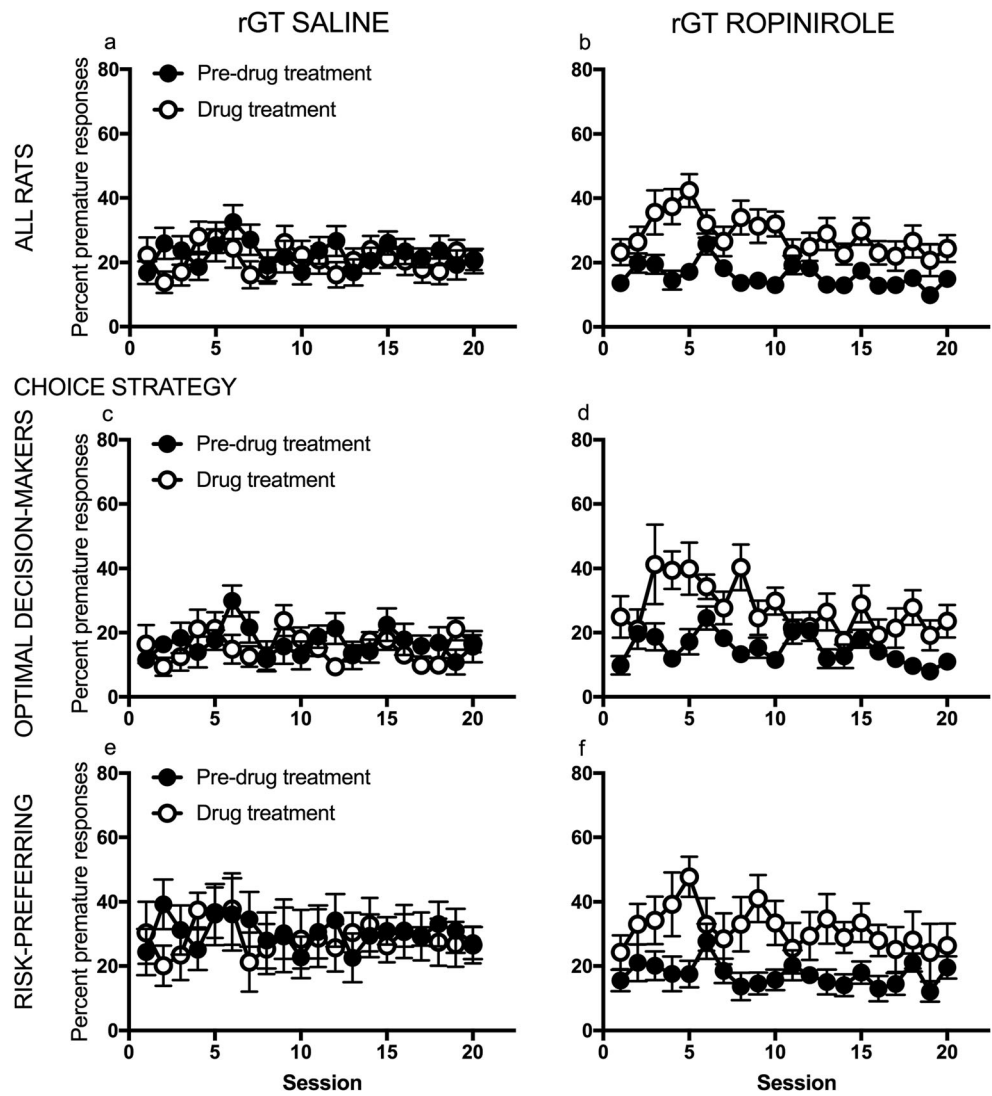
week of ropinirole treatment was compared to baseline (Fig. 4; drug treatment × time point, week 1 vs baseline: $F_{1, 36} = 5.55$, $p = 0.024$; weeks 2–4 vs baseline: all $F_s < 1.67$, all $p_s > 0.205$, NS). These data suggest that chronic ropinirole initially destabilized choice preference in a small and inconsistent manner, but there was no lasting change in choice patterns.

Nonchoice variables Chronic ropinirole dramatically increased premature responding in all rats performing the cued rGT, regardless of individual differences in choice strategy. Although this effect diminished in magnitude over time, it remained significant for the duration of drug administration (Fig. 5a, b; drug treatment—week 1: $F_{1, 36} = 62.68$, $p < 0.001$; all other weeks: $F_s > 14.58$, all $p_s < 0.001$; Fig. 5c–f; drug treatment × choice strategy: all $F_s < 0.97$, all $p_s > 0.331$, NS). In contrast to the standard rGT, risk-preferring rats made more premature responses on the cued rGT at baseline compared to optimal decision-makers, but this difference between the groups was no longer evident during treatment with ropinirole (baseline choice strategy: $F_{1, 36} = 4.70$, $p = 0.037$; weeks 1–4 choice strategy: all $F_s < 3.43$, all $p_s > 0.072$). Similar to the data from the uncued version of the task, choice behavior at baseline did not predict the number of premature responses made following chronic ropinirole ($F_{1, 18} = 0.18$, $p = 0.676$, $R^2 = 0.010$, NS).

Data values for all other nonchoice variables are given in Table 5. Ropinirole decreased the number of omissions, an effect that was evident from the second week of drug treatment and did not depend on individual choice

strategy (drug treatment—week 1: $F_{1, 36} = 2.04$, $p = 0.162$, NS; week 2: $F_{1, 36} = 11.70$, $p = 0.002$; week 3: $F_{1, 36} = 4.910$, $p = 0.033$; week 4: $F_{1, 36} = 6.911$, $p = 0.013$; choice strategy: all $F_s < 2.103$, all $p_s > 0.156$, NS; drug treatment × choice strategy: all $F_s < 2.032$, all $p_s > 0.163$, NS). Chronic ropinirole also decreased the latency to choose an option, once again independent of whether rats were classified as risk-preferring or optimal decision-makers (drug treatment—week 1: $F_{1, 36} = 8.76$, $p = 0.005$; week 2: $F_{1, 36} = 13.27$, $p = 0.001$; week 3: $F_{1, 36} = 15.62$, $p < 0.001$; week 4: $F_{1, 36} = 19.80$, $p < 0.001$; choice strategy: all $F_s < 1.87$, all $p_s > 0.180$, NS; drug treatment × choice strategy: all $F_s < 1.29$, all $p_s > 0.263$, NS). Similar to the uncued rGT, risk-preferring rats were faster at collecting reward at baseline, and this effect remained unchanged during treatment with ropinirole (choice strategy baseline: $F_{1, 36} = 19.61$, $p < 0.001$; all other: $F_s > 5.41$, all $p_s < 0.026$; drug treatment: all $F_s < 3.48$, all $p_s > 0.070$, NS). Optimal decision-makers again performed more trials, once again likely due to the more frequent occurrence of longer punishments arising from risky rats' preference for the disadvantageous options (baseline choice strategy: $F_{1, 36} = 41.81$, $p < 0.001$). However, ropinirole treatment decreased the number of trials performed during the first week of treatment, regardless of the animals' choice preference, likely due to the dramatic increase in premature responses observed during this time point. This effect disappeared by week 2 of chronic administration (drug treatment—week 1: $F_{1, 36} = 10.16$, $p = 0.003$, all other weeks: $F_s < 3.36$, all $p_s > 0.075$, NS).

Fig. 3 Premature responses on the uncued rGT during chronic ropinirole. Chronic ropinirole increased premature responding during the first week of chronic ropinirole on the uncued rGT, regardless of baseline choice strategy. Data is shown predrug treatment and during drug treatment. Percent premature response made in the saline-treated rats (a) and in ropinirole-treated rats (b). Premature responses made in the optimal decision-makers (c, d) and in risk-preferring animals (e, f). Data shown are mean ± SEM



Discussion

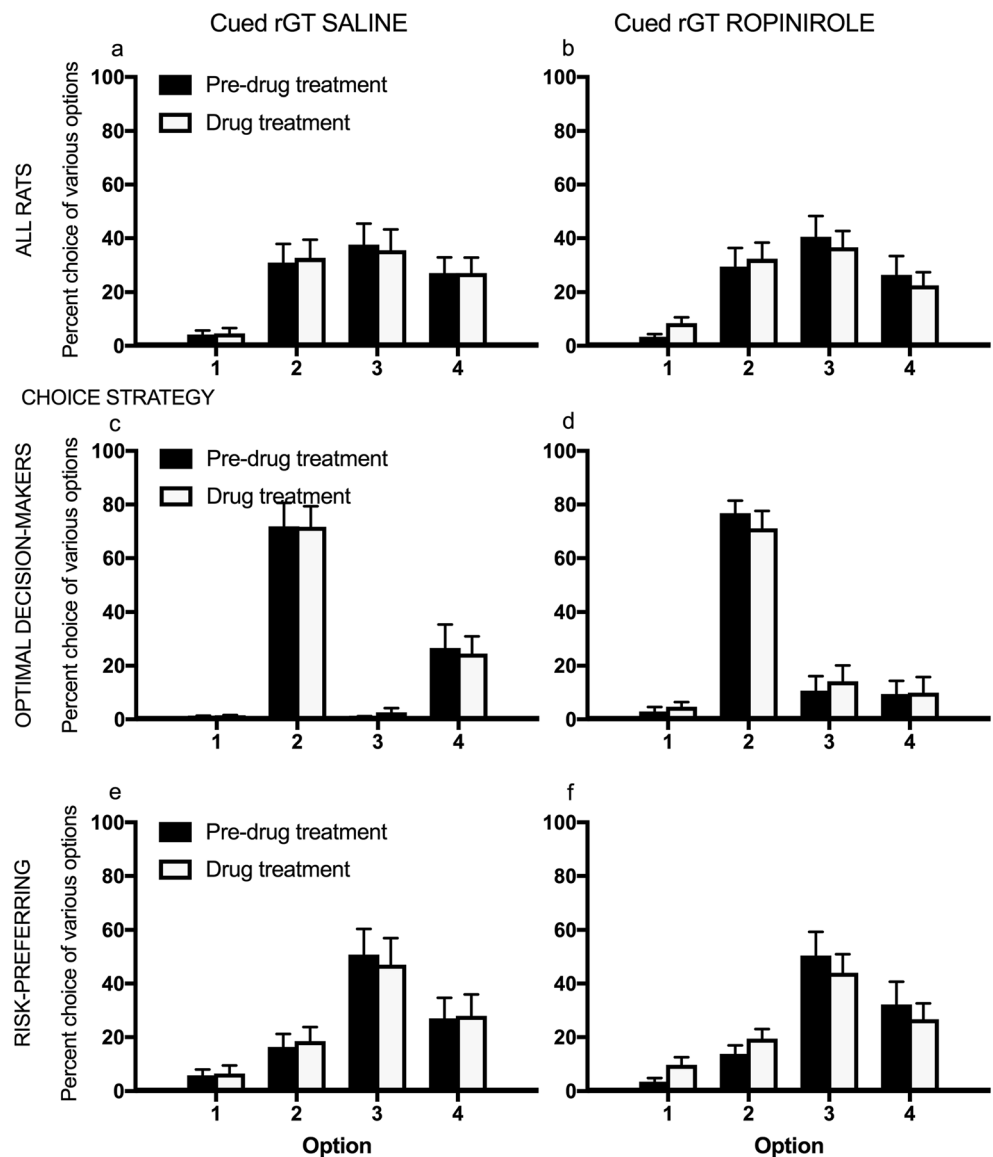
Here, we report that chronic slow-release administration of the dopamine D_{2/3} agonist ropinirole reduces omissions and increases motor impulsivity in rats performing the rGT. Surprisingly, this latter effect was much more pronounced when wins were paired with audiovisual stimuli. However, these drug-induced increases in premature responding and

motivation were not accompanied by an increase in risky choice in either the cued or uncued rGT. Such a null effect on decision-making contrasts with previous demonstrations that the identical drug treatment can potentiate choice of uncertain outcomes in a rat model of risk aversion (Tremblay et al. 2017). Collectively, these findings suggest that not all mental processes relating to decision-making under uncertainty and impulse control are equally affected by chronic

Table 3 Other measurements on the rGT during chronic ropinirole

	Premature responses	Choice latency	Collection latency	Omission	Trials
Saline Risk-preferring	28.15 ± 7.18	1.12 ± 0.21	0.68 ± 0.04	0.24 ± 0.18	64.48 ± 9.37
Saline Optimal decision-makers	14.08 ± 2.38	0.89 ± 0.10	0.88 ± 0.05	0.49 ± 0.27	110.94 ± 9.06
Ropinirole Risk-preferring	26.39 ± 7.33	0.74 ± 0.17	0.69 ± 0.16	0.10 ± 0.10	60.47 ± 4.83
Ropinirole Optimal decision-makers	20.33 ± 5.25	0.75 ± 0.07	1.12 ± 0.08	0.13 ± 0.11	125.33 ± 10.33

Fig. 4 Choice behavior on the cued rGT during chronic ropinirole. Chronic ropinirole destabilized choice behavior on the cued rGT. Data is shown predrug treatment and during drug treatment, but this did not depend on baseline preference. Percent choice of the various options in the saline- (a) and ropinirole-treated animals (b). Percent choice of the various options in the optimal decision-makers (c, d) and in risk-preferring rats (e, f). Data shown are mean \pm SEM



dopamine agonist therapy. This pattern of results may therefore offer valuable insight into the cognitive mechanism underlying the family of iatrogenic impulse control and addiction disorders that can result from this class of medications.

In addition to the changes in gambling-related behavior documented in response to chronic ropinirole, chronic pramipexole delivered via minipump or twice-daily injections also increased the choice of uncertain options in a probability discounting task (Holtz et al. 2016; Rokosik and Napier 2012) and increased compulsive responding in a contrafreeloading task (Schepisi et al. 2013). Acute administration of pramipexole also tended to increase impulsive choice, as indicated by greater choice of the smaller-sooner reward in delay discounting paradigms (Madden et al. 2010). In all three decision-making tasks sensitive to pramipexole or ropinirole administration, the contingencies therefore shift such that the optimal lever to press varies over the course of the session,

whereas the optimal choice remains constant throughout the rGT. As discussed by Madden et al. (2010), this would result in stronger stimulus–outcome, and action–outcome, associations on the rGT, which may render behavior less sensitive to perturbation by pharmacological challenge (Laties 1975; Laties and Weiss 1966; Moerschbaecher et al. 1979).

However, numerous studies have shown that choice patterns on the rGT are mutable by a variety of monoaminergic and catecholaminergic ligands (e.g., Adams et al. 2017a; Baarendse et al. 2012; Di Ciano et al. 2018; Silveira et al. 2015; Zeeb et al. 2009). Choice on the uncued version of the rGT is sensitive to reinforcer devaluation, as would be expected if behavior was truly goal-directed rather than habitual or automatic (Zeeb and Winstanley 2013). Furthermore, stable patterns of decision-making on the rGT can be altered by concurrent cocaine self-administration: risky choice is further amplified in animals identified as risk-preferring at baseline,

Table 4 Choice behavior on the cued rGT during chronic ropinirole

	Option	Time point				
		Predrug treatment	Week 1	Week 2	Week 3	Week 4
Saline Risk-preferring	P1	5.82 ± 2.14	6.48 ± 2.98	5.95 ± 2.40	7.31 ± 2.96	8.77 ± 3.30
	P2	16.34 ± 4.86	18.52 ± 5.29	15.88 ± 4.85	17.97 ± 5.78	18.50 ± 5.79
	P3	50.82 ± 9.54	47.00 ± 9.92	46.27 ± 9.73	42.24 ± 9.50	41.96 ± 9.32
	P4	27.02 ± 7.69	28.00 ± 7.94	31.91 ± 8.05	32.48 ± 7.96	30.77 ± 7.82
Saline Optimal decision-makers	P1	0.81 ± 0.60	1.08 ± 0.56	0.98 ± 0.53	0.79 ± 0.69	0.53 ± 0.34
	P2	71.85 ± 8.79	71.70 ± 7.68	78.70 ± 6.47	76.68 ± 6.84	78.93 ± 6.49
	P3	0.68 ± 0.56	2.66 ± 1.53	2.22 ± 1.24	4.26 ± 2.54	4.27 ± 3.24
	P4	26.65 ± 8.76	24.55 ± 6.45	18.10 ± 5.34	18.27 ± 5.00	16.27 ± 4.53
Ropinirole Risk-preferring	P1	3.52 ± 1.24	9.75 ± 2.78	14.69 ± 4.74	10.10 ± 3.84	10.52 ± 3.72
	P2	13.83 ± 3.12	19.48 ± 3.57	15.82 ± 4.36	15.43 ± 4.40	13.94 ± 3.66
	P3	50.49 ± 8.84	44.07 ± 6.93	45.08 ± 8.04	47.89 ± 8.65	44.14 ± 8.46
	P4	32.17 ± 8.56	26.71 ± 5.93	24.41 ± 7.05	26.58 ± 7.84	31.41 ± 8.15
Ropinirole Optimal decision-makers	P1	2.96 ± 1.63	4.74 ± 1.71	5.42 ± 3.12	7.49 ± 4.98	6.58 ± 5.89
	P2	76.81 ± 4.61	71.09 ± 6.57	69.52 ± 12.70	62.96 ± 11.12	67.84 ± 13.86
	P3	10.75 ± 5.38	14.18 ± 5.97	9.84 ± 6.66	13.13 ± 6.38	12.23 ± 7.78
	P4	9.48 ± 4.88	9.99 ± 5.78	15.22 ± 9.05	16.42 ± 10.11	13.35 ± 7.97

and this increase in risk preference predicted greater cue-induced drug-seeking (Ferland and Winstanley 2016). Such data compromise the argument that choice on the rGT fails to capture decision-making processes of theoretical relevance to addiction disorders. Furthermore, PD patients with impulse control disorders are not necessarily impaired on the IGT (e.g., Bentivoglio et al. 2013; Euteneuer et al. 2009), although patients with substance use disorder consistently exhibit greater risky choice (Bechara 2005; Bechara et al. 2001; Bolla et al. 2005; Goudriaan et al. 2005; Grant et al. 2000; Stevens et al. 2013; Verdejo-Garcia and Bechara 2009; Wang et al. 2013). As such, the decision-making profile of addiction vulnerability may be dissociable from that related to iatrogenic impulse control disorders (see discussion in Winstanley and Clark 2016).

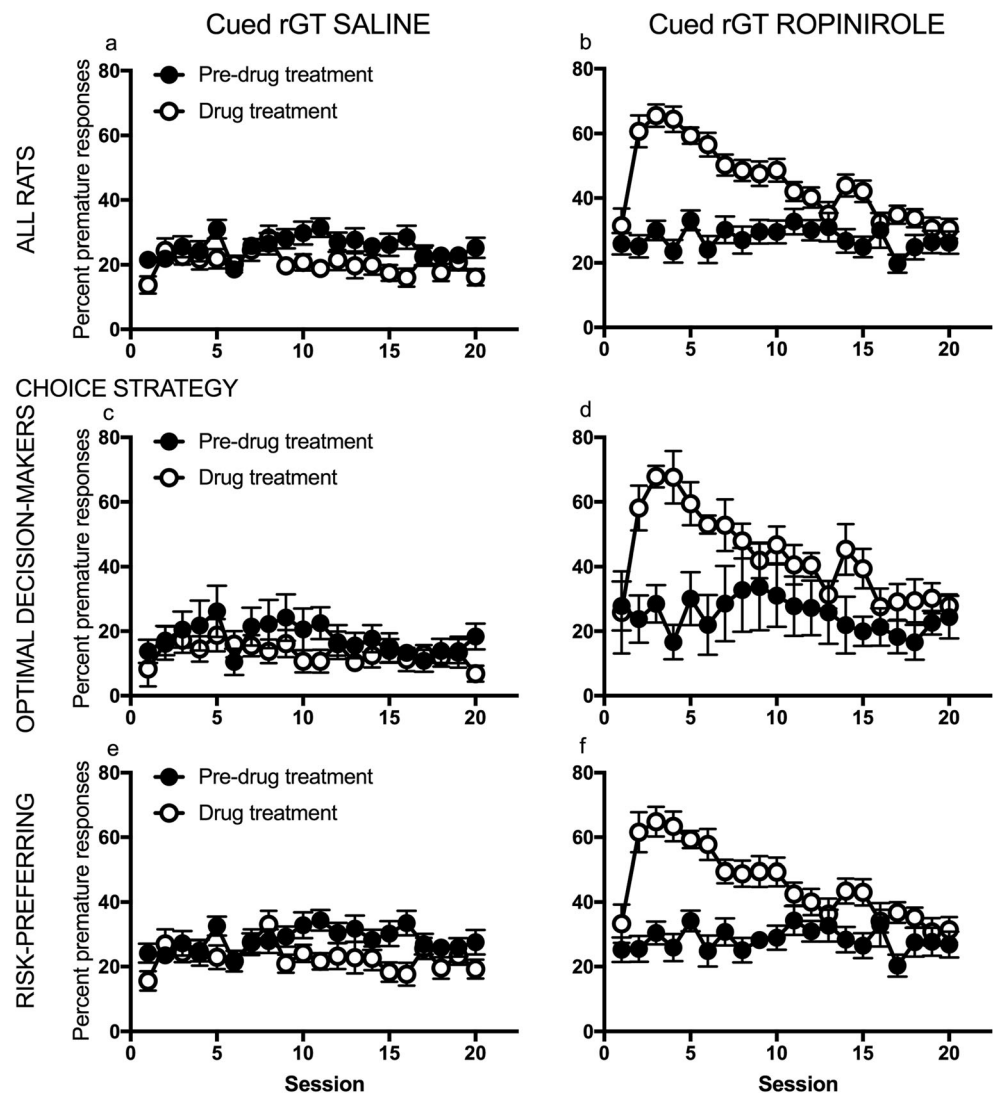
One major limitation of the current study is the use of a single dose of ropinirole. Although it is not uncommon for behavioral studies that use chronic dosing to take such an approach, it is nevertheless not ideal. We have previously reported null effects of a range of acute doses of other D_2 family agonists on choice using standard Latin square drug designs (quinpirole, bromocriptine; Zeeb et al. 2009), but chronic dosing may well induce distinct effects. In terms of increasing the dose to try and detect an effect on choice, sufficient drug to last 28 days must be dissolved in only 2 ml of physiological saline. Although ropinirole is soluble up to 133 mg/ml in water, its solubility drops in ionic solvents (Li et al. 2016). Extrapolating from these published data using 1 M saline, it would probably be possible to deliver up to 10 mg/kg/day, but the concentration used here is

already much greater than that used to treat patients (max 24 mg/day (Nashatizadeh et al. 2009), equating to 0.3 mg/kg for an 80-kg human).

However, ropinirole is subject to hepatic clearance, and this process is considerably faster in rodents. While the half-life of oral ropinirole is 5–6 h in humans, it is only 30 min in a rat (Ramji et al. 1999). Daily bolus dosing (1 mg/kg) for 10–21 days has been used to test the efficacy of ropinirole in both reducing the motor symptoms of PD and precipitating motor side effects in rodents (Eden et al. 1991; Lane and Dunnett 2010; Prikhojan et al. 2000), although modest beneficial effects have also been observed at doses as low as 0.2 mg/kg (Matsukawa et al. 2007; Ravenscroft et al. 2004). Changing the route of administration and switching from bolus to slow-release formulations will also alter the pharmacokinetics of the drug. T_{max} with transdermal application of ropinirole in a rat was approximately 5–6 times greater than that observed after the same dose was administered via oral tablet (1.1 mg/kg; Azeem et al. 2012). Faster clearance and slower T_{max} therefore justify the use of higher slow-release doses in rats as compared to humans. However, using a slow-release dose no more than 5–6 times higher than that typically used in bolus formulations to induce anti-parkinsonian effects seems like an appropriate upper limit using osmotic minipumps, particularly given the concerns over toxicity and drug accumulation that can occur with chronic dosing (Endrenyi and Tothfalusi 2012; Tothfalusi and Endrenyi 2003).

Increasing the dose to try and induce risky decision-making on the rGT is therefore difficult to justify as a model of iGD, particularly as we have reliably shown that 5 mg/kg/day is

Fig. 5 Premature responses on the cued rGT during chronic ropinirole. Chronic ropinirole potentially increased premature responding on the cued rGT, regardless of baseline choice strategy. Data is shown predrug treatment and during drug treatment. Percent premature responding in the saline-treated rats (a) and in ropinirole-treated rats (b). Premature responses made in the optimal decision-makers (c, d) and in risk-preferring animals (e, f). Data shown are mean \pm SEM



sufficient to induce marked increases in preference for uncertain outcomes in another decision-making paradigm (Tremblay et al. 2017). Furthermore, this dose was sufficient here to produce a marked increase in premature responding on the cued rGT, albeit only a transient increase in the uncued version of the task, suggesting that impulsivity can be sustainably elevated at this dose but only if cues are present. As such, this may be close to a “threshold” dose for precipitating lasting changes in motor

impulsivity, such that lower doses would be ineffective. Further work is currently planned to test this prediction.

Ropinirole’s effects on impulsivity argue against any suggestion that the osmotic minipumps were not releasing drug, so why did we not observe the expected increase in risky choice? One potentially critical feature of the rGT is absent from the decision-making tasks previously shown sensitive to pramipexole or ropinirole: nonrewarded trials result not only

Table 5 Other measurements on the cued rGT during chronic ropinirole

	Premature responses	Choice latency	Collection latency	Omission	Trials
Saline Risk-preferring	24.03 \pm 3.24	1.69 \pm 0.24	0.59 \pm 0.04	1.32 \pm 0.49	62.07 \pm 3.06
Saline Optimal decision-makers	16.55 \pm 3.40	1.52 \pm 0.09	0.86 \pm 0.08	2.24 \pm 0.65	81.80 \pm 15.34
Ropinirole Risk-preferring	61.37 \pm 3.72	0.99 \pm 0.10	0.61 \pm 0.04	0.68 \pm 0.56	42.24 \pm 2.54
Ropinirole Optimal decision-makers	61.21 \pm 4.23	0.68 \pm 0.12	0.80 \pm 0.03	0.08 \pm 0.08	57.96 \pm 5.36

in the omission of something appetitive, but also an aversive event. As reviewed recently (Winstanley and Floresco 2016), the inclusion of this negative consequence, designed to explicitly signal loss as opposed to failure to gain, may alter the neuronal circuitry and neurotransmitter systems mediating decision-making. It is therefore possible that $D_{2/3}$ agonists amplify the choice of uncertain outcomes under conditions in which anticipated gains are strongly signaled, or the potential negative consequences are less salient. Demonstrating that ropinirole likewise fails to amplify risky choice on the risk discounting task, in which losses are signaled by an electric shock (Simon et al. 2009), would be a useful preliminary test of this hypothesis.

All the decision-making tasks shown sensitive to $D_{2/3}$ agonist treatment are also essentially binary choice tasks, whereas animals choose between four options in the rGT. This increased complexity may fundamentally alter computation, increasing the number and nature of neural systems recruited into the choice process and potentially generating some redundancy. It is certainly possible that manipulating certain circuits or neurotransmitter systems may have less behavioral impact on the rGT due to more distributed control (Cocker and Winstanley 2015; Floresco et al. 2008; Winstanley and Clark 2016; Winstanley et al. 2006, 2010a). For example, the psychostimulant amphetamine, which blocks the reuptake of multiple monoamines, increases the choice of P1 and decreases the choice of P2 on the uncued rGT, yet this effect cannot be reproduced by selective dopamine, noradrenaline, or serotonin (5-HT) reuptake inhibitors (Baarendse et al. 2012; Zeeb et al. 2009). However, co-administration of any two of these latter agents can partially or completely reproduce amphetamine's effects (Baarendse et al. 2012).

Nevertheless, an increase in preference for P3 was observed in the cued rGT following administration of a ligand highly selective for a single receptor, the D_3 receptor agonist PD168907 (Barrus and Winstanley 2016). Indeed, based on this latter finding, we might have expected chronic ropinirole to likewise increase risky choice on the cued rGT without affecting premature responding, and yet we saw the opposite profile of effects. The results of chronic ropinirole administration also contrast sharply with acute bolus administration of a range of D_2 family agonists on the rGT and 5CSRT, none of which increase premature responding (Winstanley et al. 2010b; Zeeb et al. 2009). This pattern of data points to two particularly important conclusions: (a) chronic slow-release administration of a compound does not necessarily have the same effect as acute bolus injections of similar ligands, and/or (b) the pro-impulsive effects of ropinirole may not arise through its D_3 agonist moiety. In support of the latter, optical stimulation of neurons expressing the D_2 receptor in the nucleus accumbens suggests that neural transmission at this receptor subtype is sufficient to regulate preference for uncertain outcomes (Zalocusky et al. 2016). However, D_2 and D_3

receptors can also form heterodimers, and activation of these receptors by pramipexole and ropinirole may play a functionally unique role in mediating ICDs following DRT treatment (Scarselli et al. 2001).

Chronic rather than acute activation of D_3 receptors, alone or in conjunction with D_2 receptors, may also alter intracellular signaling so as to uniquely modulate reward-motivated behaviors. Prolonged stimulation of the D_2 receptor results in site-specific decreases in phosphorylation of Akt (Thr 308), a serine/threonine kinase that negatively regulates glycogen synthase kinase 3α and β (GSK3 α/β), via a β -arrestin-dependent mechanism (Beaulieu et al. 2004, 2005, 2007). Both of these pathways have been implicated in neuroplasticity (Grimes and Jope 2001; Li and Gao 2011; Lonze and Ginty 2002) and may be relevant for the mechanism through which chronic $D_{2/3}$ agonists trigger impulse control deficits.

The presence of audiovisual win-paired cues clearly potentiated the ability of ropinirole to enhance motor impulsivity, although how this happens remains unclear. The monoaminergic tone of the rat brain may be significantly different when engaged in the cued vs uncued rGT, as suggested by differential drug effects across the two task variants (Adams et al. 2017a; Barrus and Winstanley 2016). The ability of d-amphetamine to enhance this form of motor impulsivity critically depends on dopamine release in the ventral striatum (Cole and Robbins 1989; Pattij et al. 2007). Cues that predict reward elicit phasic bursts of activity in dopaminergic neurons, and uncertainty regarding whether reward will be delivered following stimulus presentation also leads to ramping up of dopaminergic activity (Fiorillo et al. 2003; Schultz 1998). Repeated exposure to cues that predict reward with maximal uncertainty, as well as responding on variable as opposed to fixed schedules of reinforcement, can sensitize rats to the hyperlocomotor effects of amphetamine (Singer et al. 2012; Zack et al. 2014; Zeeb et al. 2017). Collectively, these data suggest that the experience of performing the cued gambling task may render behavior more sensitive to dopamine agonists due to neuroplastic processes within the dopamine system.

However, a recent study suggests that the increase in preference for uncertain rewards caused by pramipexole cannot be explained by the ability of this drug to blunt changes in phasic dopamine release (Pes et al. 2017). Yohimbine, an α_2 adrenoceptor antagonist which results in disinhibition of noradrenergic neurons through blockade of autoreceptors, increases premature responding on the 5CSRT through noradrenergic mechanisms (Adams et al. 2017b; but see also Mahoney et al. 2016). Furthermore, it is well-documented that salient sensory stimuli potently activate phasic activity within the noradrenergic system (Aston-Jones and Cohen 2005; Usher et al. 1999), such that the cued rGT may theoretically elicit greater noradrenergic activity. Within the nucleus accumbens, noradrenaline can direct the release of dopamine

through both activation of beta receptors and inhibition of alpha receptors (Meyer et al. 2014), and the beta receptor antagonist propranolol partially attenuated the increase in task engagement caused by chronic ropinirole in a rodent slot machine task (Cocker et al., in press). Whether propranolol can likewise attenuate the increase in premature responding observed on the cued or uncued rGT remains to be determined.

The 5-HT and dopamine systems also work together to regulate impulsivity; forebrain depletion of serotonin increases premature responding and prevents amphetamine from exerting any further pro-impulsive effects (Harrison et al. 1997a, b). Increasing transmission through 5-HT_{2A} receptors increases impulsive action, whereas potentiating activity at 5-HT_{2C} receptors has the opposite effect (Higgins et al. 2003; Winstanley et al. 2004), and the balance of signaling through these two receptor subtypes may regulate the expression of motor impulsivity (Anastasio et al. 2015; Cunningham and Anastasio 2014). Chronic administration of pramipexole via the osmotic minipump increased the firing rate of serotonergic neurons (Chernoloz et al. 2011). Recent data demonstrate that a 5-HT_{2A} antagonist and 5-HT_{2C} agonist can decrease premature responding on both the cued and uncued rGT (Adams et al. 2017a). The highly selective 5-HT_{2A} antagonist pimavanserin is already used to treat psychosis in PD; therefore, this could be a particularly promising adjunctive therapeutic to target iatrogenic impulsivity.

The potential for dopaminergic medications to induce gambling disorder and impulse control problems can significantly limit their therapeutic potential, and a better understanding of the neurocognitive processes underlying the precipitation of such psychiatric side effects may help in their treatment and prevention. Here we show that chronic ropinirole did not increase risky decision-making on the rGT, perhaps due to the salient loss signals incorporated into the task, or the complexity of the decision space. However, chronic ropinirole did exacerbate motor impulsivity, and this deficit in impulse control is amplified in the presence of win-paired cues. High impulsivity is a well-documented vulnerability factor for gambling disorder (Petry 2001; Verdejo-García et al. 2008). Recent data suggest that higher levels of motor impulsivity and negative urgency were specifically associated with problematic low-stakes machine gambling, perhaps due to the relative ease with which such machines can be accessed and the structural characteristics of machine play which facilitate game engagement (frequent payouts, losses disguised as wins, near-misses, etc.; Lutri et al. 2018). Although impulsiveness was not associated with a preference for more rapid rates of play on a simulated EGM (Worhunsky and Rogers 2018), more impulsive individuals showed greater (suboptimal) probability distortions when learning action values in a probabilistic reinforcement-learning game (Lim et al. 2015). As such, greater impulsivity may render individuals more vulnerable to pathological EGM play, in which sensory cues and

other devices are designed to obscure the probability of positive or negative outcomes (Alter 2017; Dixon et al. 2010; Dow Schull 2012). The potential for sensory stimulation to interact with drug treatments to facilitate maladaptive behaviors warrants serious consideration with regard to psychiatric vulnerability, particularly with regard to addiction disorders and electronic game development.

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Compliance with ethical standards

Conflict of interest In the past 3 years, CAW has consulted for Hogan Lovells LLP and received due compensation. The authors confirm they have no other conflicts of interest or financial disclosures to make.

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