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Pramipexole enhances disadvantageous decision-making: Lack of relation to changes in phasic dopamine release

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ABSTRACT

Pramipexole (PPX) is a high-affinity D_2-like dopamine receptor agonist, used in the treatment of Parkinson's disease (PD) and restless leg syndrome. Recent evidence indicates that PPX increases the risk of problem gambling and impulse-control disorders in vulnerable patients. Although the molecular bases of these complications remain unclear, several authors have theorized that PPX may increase risk propensity by activating presynaptic dopamine receptors in the mesolimbic system, resulting in the reduction of dopamine release in the nucleus accumbens (NAcc). To test this possibility, we subjected rats to a probability-discounting task specifically designed to capture the response to disadvantageous options. PPX enhanced disadvantageous decision-making at a dose (0.3 mg/kg/day, SC) that reduced phasic dopamine release in the NAcc. To test whether these modifications in dopamine efflux were responsible for the observed neuroeconomic deficits, PPX was administered in combination with the monoamine-depleting agent reserpine (RES), at a low dose (1 mg/kg/day, SC) that did not affect baseline locomotor and operant responses. Contrary to our predictions, RES surprisingly *exacerbated* the effects of PPX on disadvantageous decision-making, even though it failed to augment PPX-induced decreases in phasic dopamine release. These results collectively suggest that PPX impairs the discounting of probabilistic losses and that the enhancement in risk-taking behaviors secondary to this drug may be dissociated from dynamic changes in mesolimbic dopamine release.

1. Introduction

Pramipexole (PPX) is a potent non-ergot dopaminergic agonist with high selectivity for D_3 receptors and, to a lesser extent, other members of the D_2-like receptor family (Mierau et al., 1995). PPX is currently approved for the treatment of motor symptoms in Parkinson's disease (PD) and restless leg syndrome (RLS) (Lieberman et al., 1997; Montplaisir et al., 1999). Although generally well-tolerated, PPX has been associated with a greater risk for problem gambling and impulse-control disorders (ICDs), such as compulsive shopping, overeating and hypersexuality (Weintraub et al., 2010).

The neurobiological basis of these sequelae remains poorly understood, but has been extensively linked to the nucleus accumbens (NAcc) (Kelley et al., 2012), the terminal field of the mesolimbic system that plays a key role in the regulation of incentive processes and risk-based decision making (Berridge, 2007; Nachev et al., 2015; Preuschoff et al., 2006). In particular,

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several authors have posited that, in PD patients treated with PPX, the development of ICDs may be triggered by the activation of D_2-like autoreceptors in mesolimbic neurons and the ensuing reduction of phasic dopamine release in the NAcc (Kapogiannis et al., 2011; Pizzagalli et al., 2008; Riba et al., 2008); in turn, this process would blunt responsiveness to rewards and paradoxically enhance risk propensity, in the attempt to normalize mesolimbic dopamine efflux.

A key experimental tool to investigate the mechanisms of risk-based decision making is afforded by probability-discounting tasks in animal models (St Onge and Floresco, 2009). Probability discounting refers to the devaluation of a safe reward in comparison with an uncertain, yet greater gain (Rachlin et al., 1991); notably, alterations in this function have been reported in patients with gambling disorders (Holt et al., 2003; Madden et al., 2009; Petry, 2012). Recent evidence suggests that PD patients with comorbid problem gambling and ICDs display impaired decision making as well as poor processing of aversive outcomes and risky contingencies (Djamishidian et al., 2010; Rossi et al., 2010). In a recent study, Rokosik and Napier (2012) showed that high doses of PPX increased the discounting of highly disadvantageous probabilistic options in rats, but did not affect probability discounting in relation to profitable options. In view of this background, we tested the effects of low doses of PPX (0.1–0.3 mg/kg, SC) in a task specifically designed to specifically capture the response to probabilistic losses in rats. Next, we investigated the neurobiological underpinnings of the neuroeconomic effects of PPX by testing the effects of this drug on dopamine efflux in the NAcc. Furthermore, to ascertain a causal nexus between the neurochemical and behavioral effects of PPX, we studied whether the neuroeconomic properties of PPX were modified by the monoamine depleter reserpine (RES), given that phasic release of dopamine in the NAcc is due to the mobilization of a storage vesicle pool specifically sensitive to this drug (Yavich and MacDonald, 2000). However, given that high RES concentrations can reduce locomotor activity and potentially interfere with the execution of operant tasks, we selected a low-dose regimen of this agent that could suppress the presynaptic actions of PPX in the NAcc without affecting baseline motor or behavioral performance.

2. Materials and methods

2.1. Animals

Three-month-old male Long-Evans rats (Charles River, Wilmington, MA, USA) were single-housed within rooms maintained at 22 ± 2 °C and 60% humidity, with a 12 h light/dark cycle (lights on at 7:00 a.m.). Following acclimation to the housing facilities, animals were handled daily for 5 min, and underwent a food-restriction regimen, which kept them at 85–90% of their free-feeding weight throughout the study. Experimental procedures began on the eighth day of food restriction. Behavioral measurements were carried out and analyzed by trained experimenters in a blinded fashion. All experimental procedures were compliant with the NIH guidelines and approved by the local IACUC.

2.2. Drugs

PPX ((*S*)-*N* ^{6}-propyl-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine; Accela Biochem, San Diego, CA, USA) was dissolved in saline (1 ml/kg) and administered 30 min prior to behavioral testing. RES (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in saline (1 ml/kg) and administered daily 22 h before behavioral testing. All drugs were administered via subcutaneous injection.

2.3. Experimental procedures

The research presented in this article encompassed two studies.

2.3.1. Study 1

We first tested the effects of PPX (0.1–0.3 mg/kg/day, SC) on probabilistic choice and locomotor activity, using a within-subject design (n = 22/group). Probability discounting was studied in a task specifically designed to test behavioral responses to different probabilistic options, ranging from neutral to highly disadvantageous.

2.3.2. Study 2

This study addressed the hypothesis that dopaminergic deficits in the NAcc may contribute to the effects of PPX on probabilistic choice. First, we verified the effects of a low-dose RES treatment (1 mg/kg/day, SC) on 1) behavioral responsiveness in probability discounting and locomotor activity; and 2) corticostriatal monoamine levels, by HPLC. After verifying that this regimen did not impact behavioral performance in rats, we assessed whether the same treatment may modify the behavioral effects of PPX, using a between-group design (n = 30). Finally, in a separate experiment, rats (n = 21) were treated with the same combinations of RES and PPX that elicited a significant increase in probabilistic choice. The effects of these two drugs on dopamine release in the NAcc were monitored by voltammetry.

2.4. Operant training and probability discounting task

Studies were based on a modified version of the probability-discounting protocol by St. Onge and Floresco (2009), specifically adapted to capture behavioral responses to different levels of disadvantageous “winning probability” (WP) (Fig. 1A and B). Animals were tested daily between 10 a.m. and 4 p.m., for 7 days/week, in operant chambers (31 × 21 × 24 cm; Med Associates, St. Albans, VT, USA), enclosed in sound-attenuating cabinets. Each chamber contained a central food receptacle from which food pellets were dispensed (45 mg; Bioserv, Frenchtown, NJ, USA), as well as one permanent lever (in the center) and two retractable levers (one on each side). Each chamber was also equipped with a fan, a house light and stimulus lights located above each side lever. All behavioral data were recorded on a PC, using custom software (Med-PC IV, Med Associates).

Training included five distinct phases (see Table 1 for further details), detailed as follows:

2.4.1. Phase 1: Acclimation

Rats were first acclimated to the operant chambers and trained to retrieve food pellets from the dispenser in a single 30-min session, during which pellets were delivered at a variable rate averaging one/min.

2.4.2. Phase 2: Fixed-ratio (FR) reinforcement

Next, each animal was trained to press the center lever within a 30-s time allotment, using a FR1 schedule of reinforcement for 50 trials. During this training, the side levers remained retracted. The FR value was gradually increased to 5, while the time allotment for each lever press was reduced to 10 s. All animals completed center-lever training within 5 sessions.

2.4.3. Phase 3: Discrete trials

In this stage, rats were trained to perform a single side lever press following 5 center lever presses. A single press on a side lever within the allotted time (30 s to start and gradually reduced to 10 s) resulted in the delivery of one food pellet. Whenever the animal

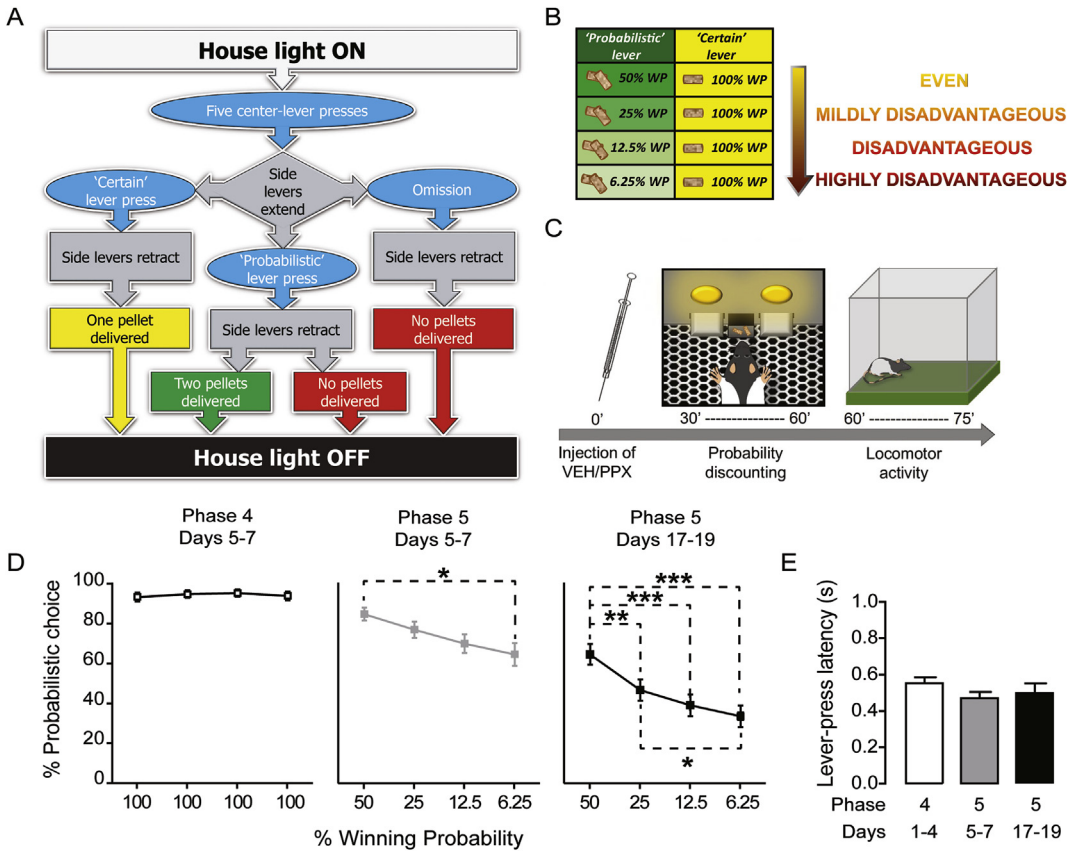

Fig. 1. Probabilistic choice training. (A) Schematic algorithm of a free-choice trial in the probability discounting task. Rats were presented with two alternative options, each associated with one lever: 1) a 'certain' option, consisting of a single pellet of food delivered after each lever press; and 2) a 'probabilistic' option, consisting of either no reward (a "loss") or a two-pellet reward (a "win"), dispensed at variable degrees of winning probability (WP, defined as the likelihood that a lever press will dispense a two-pellet food reward). (B) Synoptic table of WPs associated with the probabilistic and certain levers throughout the four blocks of the probability-discounting session. The alternatives ranged from neutral (50% WP for two pellets vs 100% WP for one pellet) to highly disadvantageous (6.25% for two pellets vs 100% for one pellet) conditions. The block sequence was presented in either an ascending or descending fashion and counterbalanced across treatment groups. Since no statistical differences were detected in block sequence presentation, data were collapsed for each WP (see text for more details). (C) Timeline of experiment. Probability discounting was tested 30′ after the injection of pramipexole (PPX) or vehicle (VEH). Following the 30′ of the operant session, rats were immediately placed in a force-plate actometer for 15′ to measure locomotor activity. (D) Probabilistic choice and (E) lever-press latency across different training stages. Data shown as mean ± SEM. *, $P < 0.05$; **, $P < 0.01$; ***$P < 0.001$. All comparisons are indicated by dotted brackets.

Table 1
Probabilistic discounting and training acquisition criteria.

Experimental phases	Acquisition criteria	Number of sessions to reach criteria
Phase 1. Acclimation	>90% food pellet retrieval	1
Phase 2. Fixed-ratio reinforcement: center lever(FR1–FR5)	>85% of animals completed 50 trials successfully for two consecutive sessions	5
Phase 3. Discrete trials: Side lever press training	>85% of animals completed 50 trials successfully for two consecutive sessions	3
Phase 4. Probabilistic lever training	>85% of animals select the probabilistic lever on >85% of free-choice trials for two consecutive sessions	6–8
Phase 5. Probabilistic discounting task	Baseline stability as a group. Assessed by one-way ANOVA for repeated measures (RP and day) as independent factors	17–21

failed to press a lever within the allotted time, the lever retracted, the house light turned off without food delivery, and the trial was scored as an omission. Each side lever was presented 25 times per session, and the order of side lever presentations was randomized across the session. Trials were separated by a 5-s intertrial interval. Rats that completed 50 successful trials/session over two consecutive sessions proceeded to the next phase.

2.4.4. Phase 4: Lever discrimination training

Throughout this phase, animals were trained to associate each of the two side levers with the assignment of either 1 or 2 pellets. Sessions consisted of 4 blocks of 20 trials (4 forced-choice trials followed by 16 free-choice trials). Each trial began with the activation of the house light, and rats were required to engage in five center lever presses in order to proceed to the forced-choice or free-choice (as appropriate) portion of the trial. During the first 4 trials of each block (forced-choice), animals were presented with only one of the two levers, associated with either 1 or 2 food pellets (dispensed upon every lever press, to consolidate the association of each lever with its respective reward value). During the remaining

16 trials (free-choice), both side levers were presented to the rat. Once a side lever was pressed, both side levers retracted, the appropriate reward (or lack thereof) was dispensed, and lights were turned off to signal the end of the trial. After each trial, the house light was extinguished for 15 s before the beginning of a new trial. Each of the two different reward sizes was consistently associated with the same lever (in a counterbalanced order) throughout the whole study. Rats proceeded to the next phase after selecting the two-pellet lever on >85% of the trials for two consecutive sessions. Animals that did not reach this criterion were omitted from the study. On average, the preference for the two-pellet lever reached full stability on day 7 of this phase, and ranged between 89.9% and 92.4% (Fig. 1D).

2.4.5. Phase 5: Probability discounting task

In this phase, rats performed the same task as in Phase 4, but the two-pellet lever delivered its associated reward in a 'probabilistic' fashion. Probabilities were associated with WPs at 50%, 25%, 12.5% and 6.25% for each block (see Fig. 1A and B), and presented in an ascending or descending fashion and counterbalanced across treatment groups. Order of presentation (ascending or descending) and associated probability were maintained throughout the study. Data referring to the two orders were collapsed, since preliminary analyses revealed no significant difference between presentation order ($F_{9,99} = 1.73$, *NS*). Conversely, the selection of the one-pellet lever (termed 'certain' from this stage onwards, to be distinguished from its 'probabilistic' alternative) always resulted in a single pellet reward after every press. To increase discriminability between WP blocks, specific differential stimuli were associated with each block (50% WP, stimulus lights continuously on; 25% WP, light flashing at 1 Hz; 12.5% WP, light flashing at 2 Hz; 6.25% WP, light flashing at 5 Hz). Presentation of discriminative stimuli were coincident with the extension of side levers during each trial block, and terminated with lever selection.

2.4.6. Probabilistic choice

Probabilistic choice was measured as the ratio of free-choice probabilistic lever selections over the total number of free-choice trials for each WP block.

Lever-press latency and number of trial omissions were also monitored; the latter parameter, however, was consistently <1/trial throughout the whole study, irrespective of treatments.

The analysis of rat behavior was complemented by a number of secondary measurements, aimed at better qualifying the phenomenology of their changes in probability discounting:

- To measure the ability of rats to distinguish between equal-probability and highly disadvantageous conditions, we calculated a *probability discrimination* index, based on the within-session differences between the probabilistic choice at 50% and 6.25% WP;
- To rule out that a greater number of selections of the probabilistic (or certain) lever may result from behavioral perseveration or stereotypies, a *repetition index* was calculated as the ratio of consecutive presses of the same lever over the total number of lever presses;
- To verify potential changes in the heuristics of risk-based decision making, the detection of significant changes in probabilistic choice was consistently followed by the analysis of "*win-stay*" and "*lose-switch*" indices, respectively calculated with the two following formulas:

Win-stay ratio = Number of 'wins' followed by the selection of the probabilistic lever/Total number of 'wins'.

Lose-switch ratio = Number of 'losses' followed by the selection of the 'certain' lever/Total number of 'losses'.

Given that our protocol was specifically designed to capture the behavioral reactivity to probabilistic losses, win-stay indices were only calculated for the block corresponding to the highest WP (50%), to avoid artefactual "ceiling effects" due to the low number of available wins in the other probabilistic blocks (4, 2 and 1, respectively).

Throughout the probability discounting task, different drug treatments were initiated when rats reached a stable baseline of behavior. Stability was analyzed using a one-way ANOVA for repeated measures using WPs and testing days as within-subject factors. Stability was achieved when the analysis of the probabilistic choice index revealed that a main effect ($P < 0.05$) for winning probabilities was not accompanied by significant effects for testing days.

2.5. Locomotor activity

Locomotor behaviors were tested immediately after operant behavior for 15 min (Fig. 1C), using square force-plate actometers (side: 42 cm; height: 30 cm) as detailed elsewhere (Fowler et al., 2001). Briefly, each force-plate actometer consisted of 4 force transducers placed at the corners of each load plate. Transducers were sampled 100 times/s, yielding a 0.01 s temporal resolution, a 0.33 g force resolution and a 1 mm spatial resolution. Timing and logging processes were performed by custom software via a LabMaster interface (Scientific Solutions, Mentor, OH, USA). Total distance travelled was calculated as the sum of the distances between coordinates of the location of center of force recorded every 0.50 s over the recording session. Vertical activity was calculated as the overall standard deviation of force applied to the plate, in relation to the body weight. Thigmotactic behaviors were measured as average distance from the nearest wall (in mm). Rotation bias was calculated by summing the locomotor turn direction over time using the center of the actometer floor as a reference point. Finally, to ascertain whether or not PPX may induce focused stereotypies, both force-time power spectra (an enhancement of power in 10–12 Hz rhythm when focused stereotypy is present) and concurrent low-movement episodes were assessed, as previously indicated (Fowler et al., 2009; Godar et al., 2016).

2.6. Spontaneous alternations in T maze

To ascertain whether changes in probability discounting may be underpinned by changes in working memory, a separate cohort of rats subjected to the same treatments were tested in a T-maze, with a variation of a previously described protocol (Bortolato et al., 2012). The T-maze consisted of a four-arm plus maze with one of the arms closed off on each trial by a removable door. Each arm was 55-cm long, 10-cm wide and 15-cm high. Briefly, each session consisted of ten consecutive trials. In each trial, rats (n = 7–8 per group) were placed in the start compartment of a T-maze. After 15 s, the door was lifted and the rat was left free to explore the two arms of the maze. As soon as the animal entered (with all four paws) one of the two alternative arms (left or right), the door of that compartment was closed for 20 s to confine the animal. The animal was then gently removed and placed again in the start compartment for the next trial. A trial was considered failed if the animal did not enter an arm within 3 min. The number of total alterations and arm visits before the first alternations was analyzed for each rat.

2.7. Voltammetry recordings in anesthetized animals

Rats were treated with an optimal drug treatment regimen that has been verified to elicit a significant increase in probabilistic choice. In particular, animals were treated with RES (or its control) for three consecutive days, followed by concomitant PPX (0.3 mg/kg, SC or its control) administration for seven days, with the last day being the day voltammetric recordings were made. Consistent with animals used in behavioral experiments, rats were food-restricted to maintain 85–90% free-feeding body weight. To conduct voltammetric measurements, rats were first anesthetized with urethane (1.5 g/kg, IP), and a stainless steel bipolar stimulating electrode (MS303/2-A; Plastics 1, Anaheim, CA, USA) and carbon fiber microelectrode (Clark et al., 2010) were stereotaxically implanted into the medial forebrain bundle (MFB) (AP −4.6 mm, ML 1.3 mm, DV 8–9.5 mm) and NAcc shell (AP 1.7 mm, ML 0.9 mm, DV −7.2 mm), respectively (Paxinos and Watson, 2005). A silver/silver chloride (Ag/AgCl) reference electrode was implanted contralateral to the recording electrode. Dopamine release was evoked by electrical stimulation of the MFB with parameters mimicking endogenous tonic and phasic firing patterns (5-Hz 30-pulse 300 μA and 30-Hz 6-pulse 300 μA, respectively) applied every five minutes in an alternating fashion. Extracellular dopamine levels were measured using fast-scan cyclic voltammetry throughout the course of the electrical stimulation protocol as previously described (Arnold et al., 2015). Once a baseline was established (defined as three consecutive responses of each stimulation type with <10% deviation from the mean), 7–10 replications of each stimulation type were carried out and used for analysis. The collected data was analyzed using software written in LabView (National Instruments).

2.8. Histological verification of voltammetric recording sites

A small lesion was created at the recording site by applying high voltage (300V) to the recording electrode for 30 s. Brains were fixed in 4% paraformaldehyde, cryoprotected in 30% sucrose solution and frozen at −80 °C. Frozen brains were sectioned (50 micron slices), stained with cresyl violet and electrode placements were assessed using a rat stereotaxic atlas (Paxinos and Watson, 2005).

2.9. Tissue preparation

Animals were sacrificed via decapitation. Brains were removed and placed in an ice-cold cutting block. Regions were dissected based on the coordinates indicated in the Paxinos and Watson rat stereotaxic atlas (Paxinos and Watson, 2005), rapidly frozen and stored at −80 °C for further processing.

2.10. High performance liquid chromatography (HPLC)

Serotonin, dopamine and norepinephrine levels in the medial prefrontal cortex, NAcc and caudate putamen were analyzed by HPLC as previously described (Bortolato et al., 2012). Samples were kept in dry ice and rapidly homogenized with an ultrasonic tissue disrupter (Sonoplus HD60, Bandelin, Germany), in a solution containing 0.1 M trichloroacetic acid, 10 mM sodium acetate, and 0.1 mM EDTA; 1 μM isoproterenol was used as an internal standard. The homogenates were centrifuged, and the supernatants were used for HPLC analysis. The mobile phase was the same as the homogenization buffer with 7% methanol for detection of serotonin. The mobile phase was filtered and deaerated, and the pump speed (Shimadzu LC-6A liquid chromatograph, Columbia, MD, USA) was 1.5 ml/min. The reverse-phase column used was a Rexchrom (Regis Technologies, Morton Grove, IL, USA) S50100-ODS C18 column with a length of 25 cm and an internal diameter of 4.6 mm. The compounds were measured at +0.7 V using a Shimadzu L-ECD-6A electrochemical detector.

2.11. Data analyses

Normality and homoscedasticity were preliminarily verified using Kolmogorov-Smirnov and Bartlett's tests. Data were analyzed with one or multiway ANOVAs followed by Newman-Keuls' test for *post-hoc* comparisons. Significance threshold was set at 0.05.

3. Results

3.1. Probability-discounting training

Rats began displaying significant differences across various WP blocks on day 4 of Phase 5 (WP: $F_{3,83} = 3.58$, $P < 0.05$; $P < 0.05$ between 50% and 6.25% WP), and reached stability on day 19 (Difference across WP blocks: $F_{3,83} = 9.67$, $P < 0.001$; Difference across days: $F_{2,166} = 1.41$, *NS*) (Fig. 1D). *Post-hoc* analyses indicated a significant reduction in probabilistic choice at 25% ($P < 0.01$), 12.5% ($P < 0.001$) and 6.25% WP ($P < 0.001$), as compared to the 50% WP block; in addition, probabilistic choice was significantly lower at 6.25% than 25% WP ($P < 0.05$). Lever-press latencies did not significantly-vary-from-Phase-4-onward-(Fig. 1E).

3.2. PPX increases the choice of highly disadvantageous options

The effects of PPX (0.1–0.3 mg/kg/day, SC) were tested on probability discounting and locomotor behavior. Since PPX administration reached a peak stability on the seventh day of treatment, the effects of this 7-day regimen were analyzed and used throughout subsequent studies. While probabilistic decision making was not affected by 0.1 mg/kg/day PPX(Treatment × WP: $F_{3,63} = 0.95$, *NS*), the daily dose of 0.3 mg/kg produced a biphasic effect on probability discounting(Treatment × WP: $F_{3,63} = 8.80$, $P < 0.001$). Indeed, while PPX induced a mild, yet significant reduction ($P < 0.05$) of the selection of levers associated with 50% WP, it increased ($P < 0.01$) probabilistic choice at 6.25% WP (Fig. 2A). These alterations reflected a significant shift in lose-switch strategy (Fig. 2B) ($F_{3,63} = 5.18$, $P < 0.01$), specifically at 50% ($P < 0.01$ and 6.25% WP ($P < 0.05$), however, no variations in win-stay parameters were detected at either dose (Fig. S1A). The biphasic response of PPX treatment to different %WP was paralleled by a significant reduction of the probability discrimination index (Fig. 2C) ($F_{1,21} = 13.98$, $P < 0.01$). While both PPX doses increased lever-pressing latency (Fig. 2D) ($F_{1,21} = 5.04$, $P < 0.05$), PPX did not induce perseverative lever-pressing patterns (Fig. S1B). Analyses of locomotor behaviors (Fig. 2E–I) revealed that PPX elicited a marked elevation in horizontal (Fig. 2E) ($F_{1,8} = 22.29$, $P < 0.01$) and vertical (Fig. 2F) ($F_{1,8} = 27.49$, $P < 0.001$) activity. Furthermore, PPX reduced thigmotaxis (Fig. 2G) ($F_{1,8} = 22.13$, $P < 0.01$) and increased rotation bias (Fig. 2H) ($F_{1,8} = 9.09$, $P < 0.05$).

3.3. Low-dose RES treatment exacerbates the effects of PPX on the propensity for probabilistic losses, but suppresses its effects on phasic dopamine release in the NAcc

Based on our results, we planned to verify whether the behavioral effects of PPX were underpinned by activation of presynaptic receptors and consequent changes in dopamine release in the NAcc. Thus, we tested whether the neuroeconomic outcomes of PPX may be affected by a concomitant low-dose RES regimen. We first found that a daily regimen of 1 mg/kg (SC) RES did not significantly affect probabilistic choice (Fig. 3A), lose-shift (Fig. 3B) and win-stay

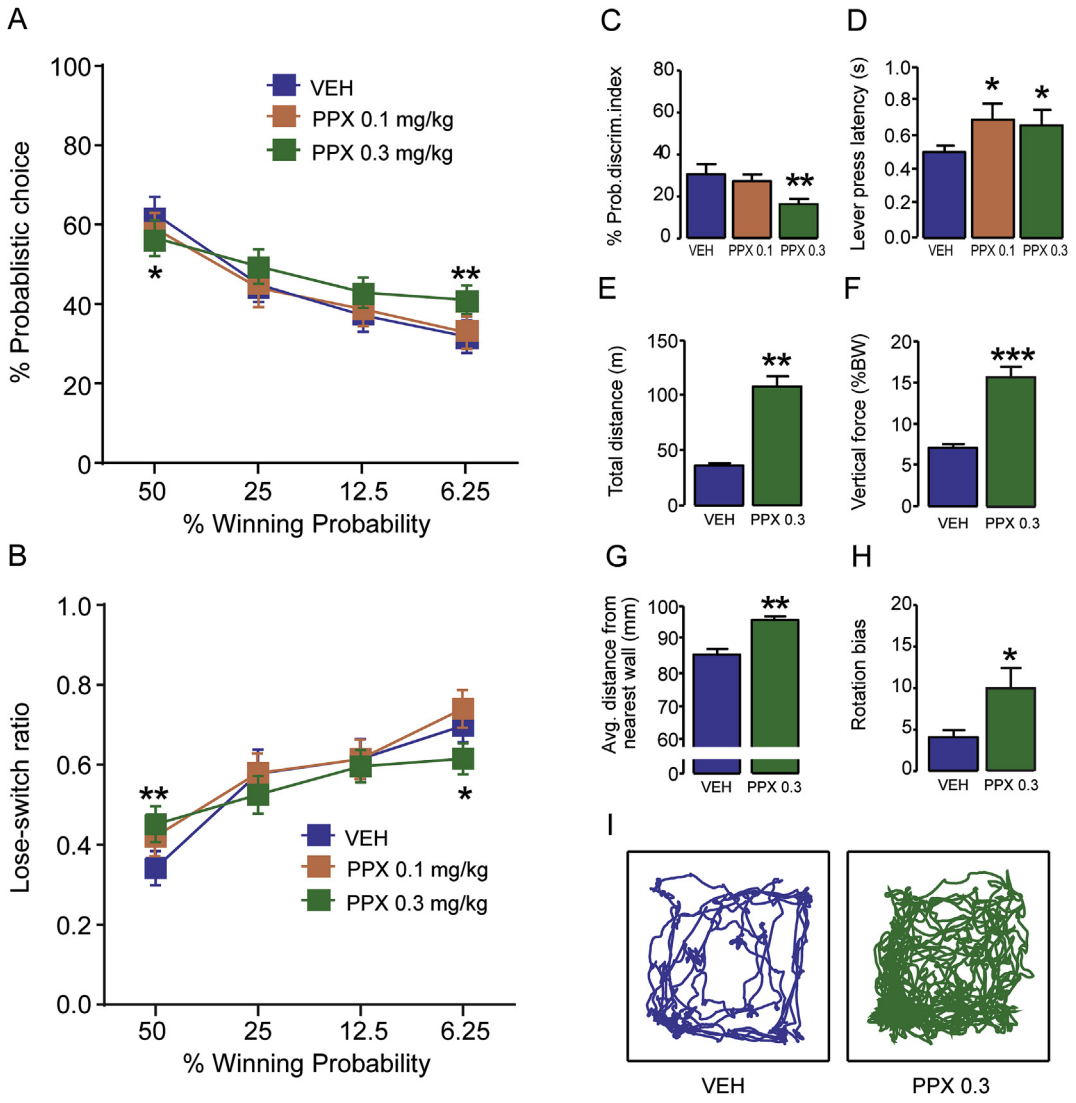

Fig. 2. Pramipexole impairs probabilistic decision making and increases locomotor activity. (A) Effects of PPX (0.1–0.3 mg/kg, SC) on probabilistic choice across the four blocks. (B–C) PPX (0.3 mg/kg, SC) affected heuristic strategies in response to negative (lose-switch) feedback and decreased probability discrimination. (D) PPX increased lever press latency. (E–H) Effects of PPX (0.3 mg/kg, SC) on locomotor activity parameters. (I) Representative tracks of locomotor pathways of rats treated with VEH or PPX (0.3 mg/kg, SC). Data shown as mean ± SEM. ***, $P < 0.001$, **, $P < 0.01$ and *, $P < 0.05$ compared to VEH-treated control.

parameters (Fig. S1C), probability discrimination index (Fig. 3C), lever-press latency (Fig. 3D), perseverative lever press behaviors (Fig. S1D) or motor behavior (Fig. 3E–H). After four days of RES treatment, rats exhibited no significant differences in monoamine content across the medial prefrontal cortex, NAcc or caudate-putamen (Fig. 4A–I), with the exception of a small, yet significant reduction in norepinephrine levels in the medial prefrontal cortex (Fig. 4B) ($F_{1,10} = 8.21$, $P < 0.05$).

We then tested whether the same RES administration regimen (1 mg/kg/day, SC) could modify the actions of PPX (0.3 mg/kg, SC) on probability discounting. Following four days of RES (or VEH) administration, rats were treated with a combination of RES and PPX (or their VEHs) for the remainder of the experiment. Locomotor activity was assessed immediately following probability discounting, with the same design used in Study 1. Three-way ANOVA revealed that PPX elicited a highly significant increase in probabilistic choice by the fourth day of PPX administration (Fig. 5A) (PPX × WP interaction: $F_{3,84} = 2799.3$, $P < 0.0001$), reaching stability after 7 days as previously identified. In addition to these effects, ANOVA disclosed a significant RES × PPX interaction at the 6.25% WP ($F_{1,28} = 4.39$, $P < 0.05$), which was verified to reflect a significant main effect of PPX ($P < 0.05$); furthermore, the effects of PPX were markedly exacerbated by RES co-treatment ($P < 0.01$). PPX treatment also elicited a main-effect on lose-shift strategies (Fig. 5B) ($F_{1,28} = 6.53$, $P < 0.05$) and a decrease in the probability discrimination index (Fig. 5C) ($F_{1,29} = 30.63$, $P < 0.001$). However, no alterations in the win-stay ratio (Fig. S1E) or perseverative lever pressing were detected (Fig. S1F). As expected, PPX increased lever-press latency irrespective of RES co-treatment (Fig. 5D) (Main PPX effect: $F_{1,29} = 6.61$, $P < 0.05$).

To ascertain that the effects of PPX and RES combination did not reflect working memory deficits, we used a separate cohort of rats to test the effects of these treatments on spontaneous alterations in a T-maze. As shown in Fig. S2, all groups engaged in equivalent numbers of alternations as well as trials before the first alternation, indicating that working memory was not affected by PPX, RES, or their combination.

The analysis of locomotor activity on treatment day 7

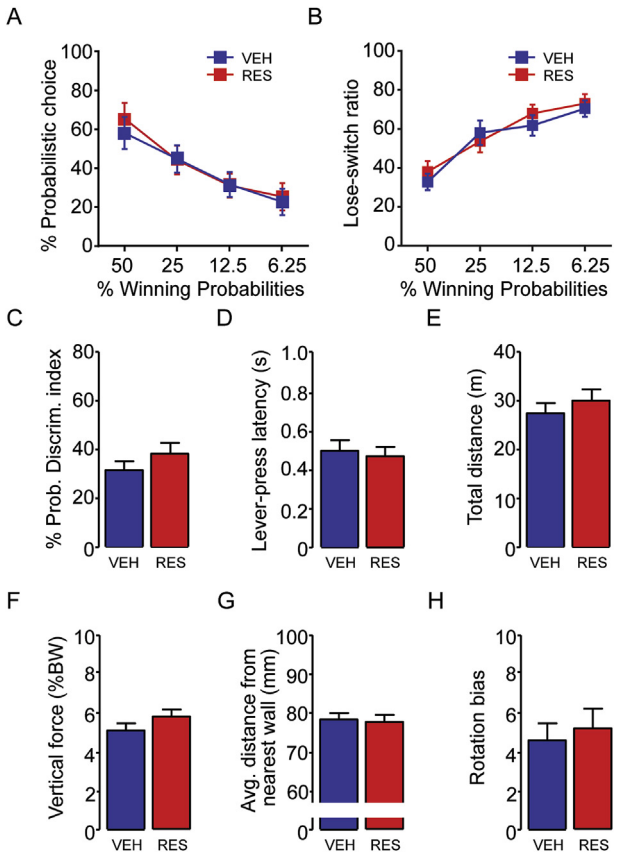

Fig. 3. Low-dose reserpine (RES, 1 mg/kg, SC) does not alter probability discounting or locomotor activity. RES (4-day treatment) had no significant effects on (A) probabilistic choice at different winning probabilities; (B) lose-switch ratio; (C) % probability discrimination index; (D) lever-press latency; and (F–H) locomotor activity parameters. Data shown as mean ± SEM. *, $P < 0.05$ compared to animals treated with vehicle (VEH).

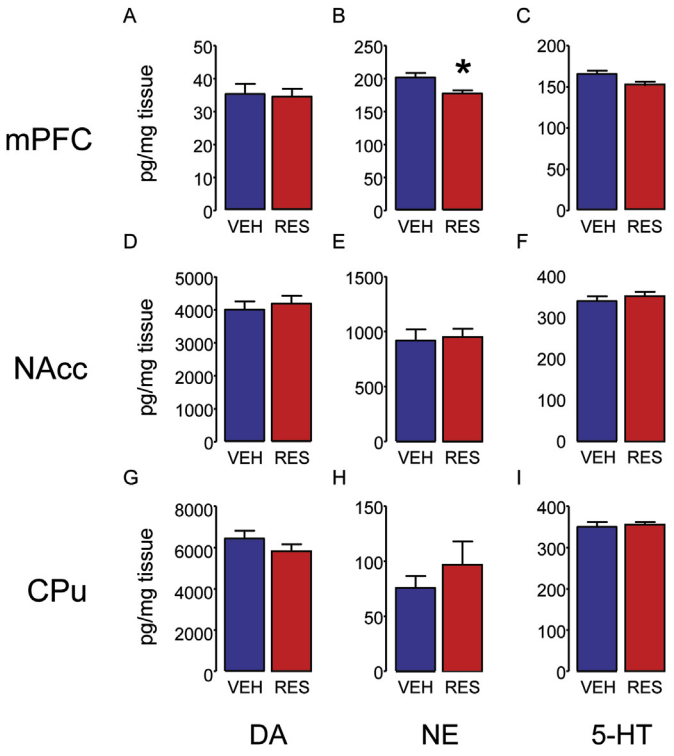

Fig. 4. Effects of reserpine (RES) on monoamine levels in the medial prefrontal cortex (mPFC), nucleus accumbnes (NAcc) and caudate putamen (CPu). (A–I) Effects of RES (1 mg/kg, SC) treatment on dopamine (DA), norepinephrine (NE) and serotonin (5-HT) levels in the mPFC, NAcc and CPu. Data shown as mean ± SEM. *P, <0.05 compared to vehicle (VEH) controls.

(Fig. 5E–K) revealed that both RES-PPX and VEH-PPX groups exhibited similar enhancements in horizontal (Fig. 5E) ($F_{1,28} = 88.14$, $P < 0.001$) and vertical activity (Fig. 5F) ($F_{1,28} = 33.11$, $P < 0.001$), as well as in the average wall distance (Fig. 5G) ($F_{1,28} = 16.75$, $P < 0.001$). These effects were not modified by RES co-administration. In addition, PPX-treated rats displayed mild, yet significant enhancements in rotation bias, as compared with their VEH-treated counterparts (Fig. 5H) ($F_{1,28} = 4.26$, $P < 0.05$). The analysis of force-time power spectra revealed that all treatment groups exhibited peaks of force frequencies at 5–7 Hz (Fig. 5I), a range associated with increased activity, but not focused stereotypies (Fowler et al., 2003). Accordingly, low-movement bouts (always associated with focused stereotypies) were significantly reduced in PPX-treated-rats, irrespective-of-RES co-treatment- ($P < 0.001$) (Fig. 5J).

To verify the impact of the combined RES-PPX treatment on the presynaptic activity of mesolimbic neurons we measured electrically evoked dopamine release in the NAcc shell of anesthetized animals using fast-scan cyclic voltammetry (Fig. 6). A significant RES × PPX interaction in phasic dopamine release was indicated by a decrease in both the area under the curve (Fig. 6A and C) ($F_{1,20} = 5.91$, $P < 0.05$) and the peak current (Fig. 6E) ($F_{1,20} = 4.12$, $P = 0.05$). *Post-hoc* analyses revealed that both RES and PPX markedly reduced dopamine phasic release ($Ps < 0.01$) and the amplitude of the peak current ($Ps < 0.01$) compared to VEH treatments. However, no significant differences were found in either parameter between rats treated with RES + VEH and RES + PPX, documenting that RES pre- and co-treatment suppressed the ability of PPX to decrease dopamine-phasic-release. Furthermore, no difference was found between VEH + PPX and RES + PPX, indicating that the presynaptic effects of PPX were not modified by RES pretreatment.

The analysis of tonic-like dopamine release evidenced that RES reduced both the area under the curve (Fig. 6B and D) ($F_{1,20} = 11.80$, $P < 0.01$) and the peak current (Fig. 6F) ($F_{1,20} = 15.68$, $P < 0.001$). While PPX had no direct effect on tonic-like dopamine release, we detected a rightward shift in the voltammetric trace (Fig. 6B), which likely reflected the-inhibition-of phasic-like dopamine release triggered by the stimulation itself.

4. Discussion

The results of this study showed that, in line with previous findings (Rokosik and Napier, 2012), PPX impaired probability discounting in rats; specifically, this drug led to a flatter probability-choice function, likely reflecting an overall reduction in the sensitivity to probability. Accordingly, PPX-treated rats engaged more in highly disadvantageous options (6.25% WP for two food pellets vs 100% WP for one food pellet, i.e., 1:8), and displayed a reduced proneness towards equally profitable alternatives (50% WP for two food pellets vs 100% for one food pellets, i.e., 1:1). The same PPX doses used in our study were found to increase impulsive choices in rats trained for delay-discounting tasks (Johnson et al., 2011, 2012; Madden et al., 2010), through impairments in the discrimination processes required for intertemporal choices (Johnson et al., 2013). Taken together, these data suggest that PPX may distort the representation of rewards and impair the ability to discern favorable from unfavorable contingencies. These

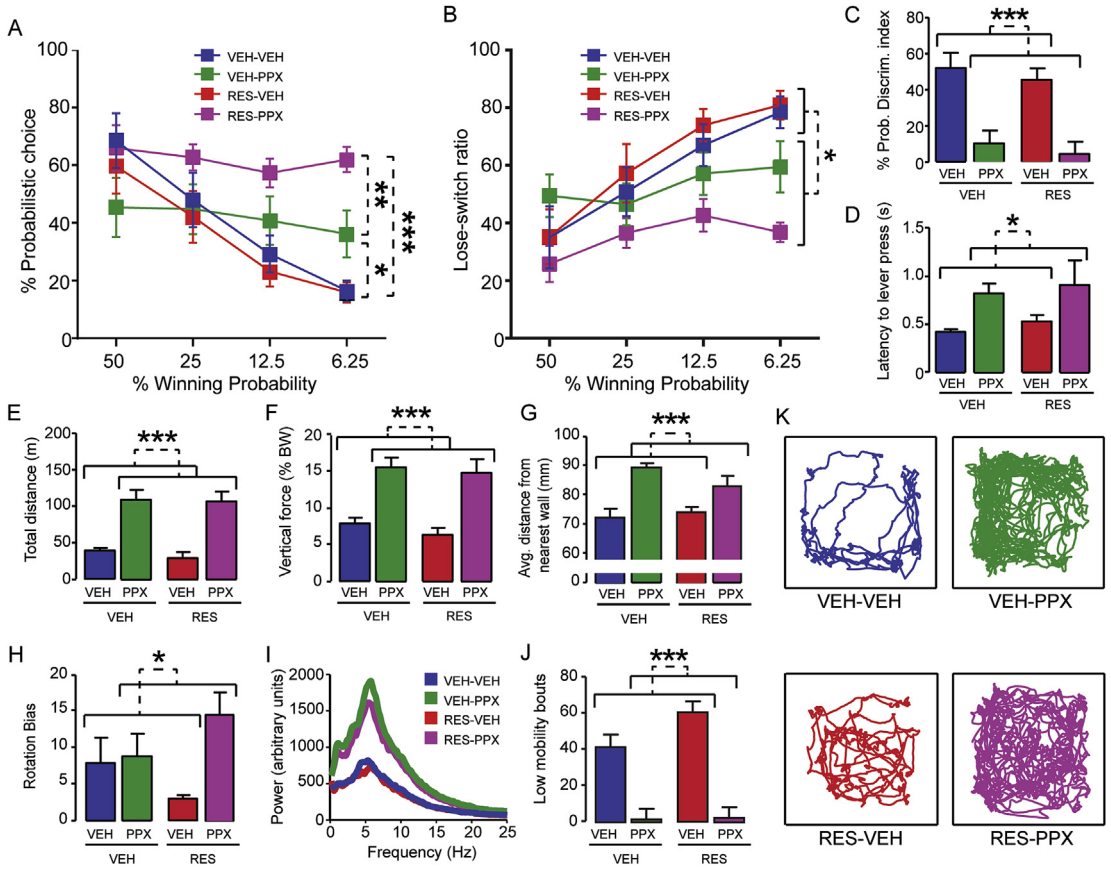

Fig. 5. Concomitant reserpine (RES) and pramipexole (PPX) treatment increases the choice of disadvantageous options. Effects of concomitant RES (1 mg/kg, SC, for 7 consecutive days) and PPX (0.3 mg/kg, SC, for the 4 last days) treatment on (A) probabilistic choice across winning probabilities (WP), (B) lose-switch strategies, (C) probability discrimination index and (D) latency to lever press. (E–K) The analysis of locomotor activity revealed that PPX increased (E) horizontal and (F) vertical activity, (G) reduced thigmotactic exploratory behavior, (H) increased rotation bias and resulted in a (J) fewer low mobility bouts, irrespective of RES co-treatment. (K) Representative locomotor path tracings of animals in each treatment group. Data shown as mean ± SEM. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. N.S., not significant. All comparisons are indicated by dotted brackets. Abbreviations: VEH, Vehicle.

neuroeconomic deficits result in a marked enhancement of disadvantageous decision making and may predispose to problem gambling and ICDs.

We found that the effects of PPX on probability discounting were accompanied by a reduction in phasic dopamine release in the NAcc; to test whether these changes in dopamine efflux directly underpinned the neuroeconomic effects of PPX, we treated rats with a concurrent low-dose RES regimen that did not affect motor or operant performance. Surprisingly, RES administration affected the neurochemical and behavioral properties of PPX in a diametrically opposite fashion. In particular, while RES fully suppressed the effects of PPX on dopamine efflux, it *increased* the choice of highly unprofitable options; specifically, the combination of PPX and RES led to an upward shift in the probability-choice curve, which abolished the effects of PPX at 50% WP and significantly increased its actions in relation to the highly disadvantageous 6.25% WP option. These findings suggest that the effects of PPX on problem gambling are not likely caused by modifications in phasic dopamine release in the NAcc.

Although our current results cannot fully explain why RES treatment exacerbated the actions of PPX on probabilistic discounting, one likely possibility may be through different effects of pre- and postsynaptic D_2-like receptors. In line with this possibility, PPX has been shown to activate both receptor subpopulations (Piercey, 1998), however, the distinct role of each in relation to specific neuroeconomic functions has been a topic of controversy. Several authors have posited that PPX may facilitate the development of ICDs in PD patients by activating D_2-like autoreceptors in relatively spared mesolimbic neurons. This mechanism would blunt reward responsiveness by reducing NAcc phasic dopamine release (Kapogiannis et al., 2011; Pizzagalli et al., 2008; Riba et al., 2008), and paradoxically enhance risk propensity, in the attempt to normalize mesolimbic dopamine efflux. In contrast, the involvement of postsynaptic targets in the behavioral effects of PPX is suggested by the fact that doses that preferentially activate presynaptic receptors do not trigger impulsive responding in healthy volunteers (Hamidovic et al., 2008). From this perspective, our results may indicate that the RES regimen used in our studies respectively attenuated and magnified the functions of pre- and post-(or extra-)synaptic D_2-like receptors in the NAcc; in turn, this conclusion suggests that PPX-induced alterations in probabilistic choice may reflect a shift in the functional balances between pre- and postsynaptic D_2-like receptors. Extreme caution, however, should be taken in drawing this inference, in the absence of confirmatory studies using microdialysis, stereotaxic microinjections in the NAcc and other brain regions. Indeed, an alternative explanation may be that the effects of PPX are mediated by alterations in dopamine efflux in other brain regions, such as the medial prefrontal cortex, which has been shown to affect probabilistic decision-making (St. Onge et al., 2011, 2012). This caveat aside, the finding that reducing presynaptic activity potentiates the effects of PPX on probability discounting suggests that hypofunctional states

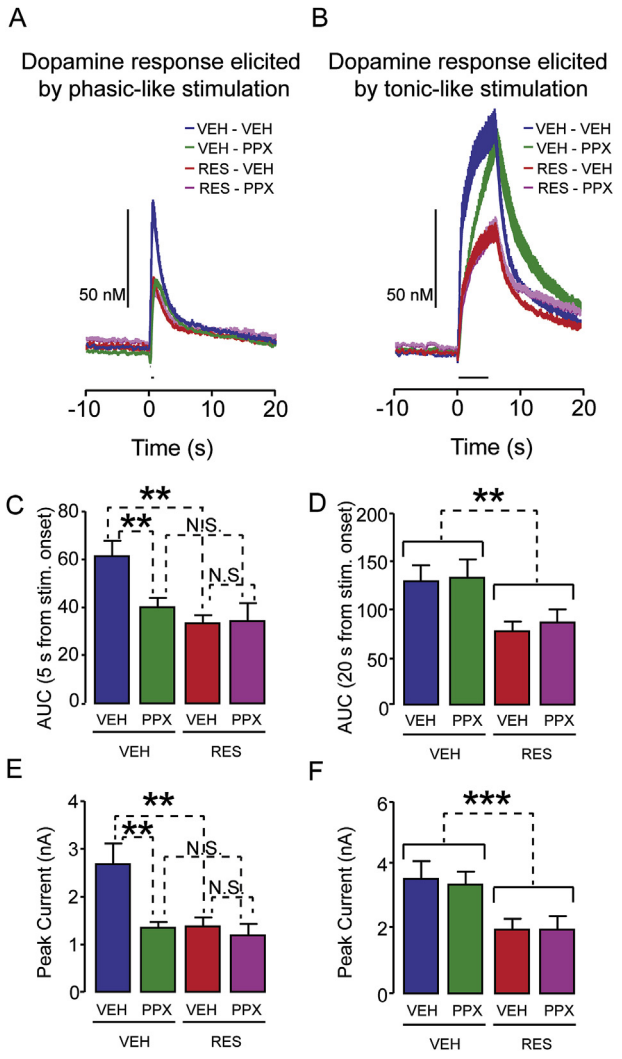

Fig. 6. Low-dose reserpine (RES) administration suppresses the effects of pramipexole (PPX) on phasic dopamine release. (A, C) Low-dose RES suppressed the inhibitory effects of PPX on phasic-like dopamine release in the NAcc shell. (A–B) Voltammetric dopamine release traces in response to electric stimulation parameters mimicking endogenous phasic and tonic firing patterns. (C–D) Area under the curve (AUC) values for phasic- and tonic-like dopamine responses. (E–F) Peak currents elicited by phasic- and tonic-like firing patterns, respectively. Response windows began at stimulation onset and ended at 5s for phasic and 20s for tonic. Black bars below traces indicate stimulation duration. Data shown as mean ± SEM. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. N.S., not significant. All comparisons are indicated by dotted brackets. Abbreviations: VEH, Vehicle.

of the mesolimbic system may increase the vulnerability for problem gambling and ICDs in response to PPX therapy. Most cases of PPX-associated gambling and ICDs have been reported in PD and RLS patients, raising the question as to whether the effects of this drug may be facilitated by pre-existing dopaminergic deficits. Notably, alterations in the mesolimbic system, albeit not pathognomonic for either PD or RLS, have been observed in a subset of patients affected by these conditions (Alberico et al., 2015; Oboshi et al., 2012); thus, these findings may suggest that deficits in the mesolimbic system may predispose to PPX-induced behavioral complications. Future analyses are warranted to verify whether animal models with lesions of the mesolimbic pathway may be more vulnerable to the adverse effects of PPX in probabilistic discounting paradigms.

The impairments in probability discounting induced by PPX were found to be unrelated to potential deficits in working memory, but likely reflected a blunted responsiveness to aversive outcomes, as attested by a marked increase in lose-switch heuristic strategies. In keeping with this concept, dopaminergic therapies have been found to alter the negative perception of losses and non-rewarded responses (Abler et al., 2009; van Eimeren et al., 2009) and disrupt learning from unfavorable outcomes (Bodi et al., 2009; Cools et al., 2006). This interpretation, however, is challenged by previous findings indicating that selective D_2 receptor activation may increase punishment sensitivity and responsiveness (Zeeb et al., 2009; Simon et al., 2011), potentially by increasing the salience of aversive cues (Killcross et al., 1997). In line with this idea, selective D_2 receptor activation in the nucleus accumbens was recently shown to signal unfavorable outcomes (Zalocusky et al., 2016). To explain this potential discrepancy, it is worth noting that the PPX doses used in our protocol should primarily activate D_3, rather than D_2 receptors. Thus, our data may suggest that D_3 receptors may mediate the observed neuroeconomic effects of PPX. This possibility is in line with recent evidence attesting that D_3 receptor activation increases the selection of highly disadvantageous options in a rat gambling task (Barrus and Winstanley, 2016); furthermore, several authors have postulated that PPX may enhance risk propensity by activating D_3 receptors in the NAcc (Matthews et al., 2004). While selective D_3 receptor activation has been shown to reduce probabilistic choices of highly advantageous (4:1) to mildly disadvantageous (1:2) options (Stopper et al., 2013), additional studies with receptor-subtype selective agonists and antagonists will be necessary to assess the role of D_3 receptors in the modulation of the response to highly disadvantageous probabilities.

The verification of a negative outcome is associated with a pause in mesolimbic firing, which enables the coding of a reward-prediction error signal (Schultz et al., 1997); however, these physiological effects are likely overridden (or at least partially masked) by pharmacological activation of D_2-like post-(or extra-)synaptic receptors in the NAcc. Thus, predominant activation of D_2-like post-(or extra-)synaptic receptors by PPX should weaken the capacity to appraise the aversive valence of a loss and obscure the discrimination of advantageous and disadvantageous outcomes. This interpretation is supported by clinical reports demonstrating deficits in reward-related learning in PPX-treated patients (Bodi et al., 2009; Pizzagalli et al., 2008).

In addition to its effects on probability discounting, PPX increased both horizontal and vertical locomotor activities and reduced thigmotaxis. PPX-induced hyperlocomotion was not influenced by RES, supporting a phenomenological dissociation between locomotor and neuroeconomic effects of PPX. Notably, although the hyperlocomotive effects of PPX were not paralleled by stereotyped behaviors, this drug enhanced rotation bias, possibly signifying a more generalized impairment in the elaboration of exploratory strategies.

Several methodological caveats should be acknowledged. First, we cannot rule out that the effects of PPX (both per se and in combination with RES) may partially reflect an impaired ability to adjust to changing probability during the operant task because our experimental sessions did not include 100% or 0% WP blocks. The exclusion of these blocks was due to the necessity of limiting each session to 30–40 min to minimize fluctuations of drug concentrations in plasma, all the while using blocks with high numbers of trials in order to test for highly disadvantageous choices. Nevertheless, this limitation is somewhat tempered by previous findings (Rokosik and Napier, 2012) showing that a higher dose regimen of PPX affected probabilistic choices between 0% and 30%, but not 100%. Second, the nonselective actions of RES do not allow us to rule out that other mechanisms may contribute to the influence of

this drug on the effects of PPX; for example, we found a mild, yet significant reduction of norepinephrine levels in the PFC. This change may partially account for some aspects of the observed decision-making deficits in rats treated with RES and PPX, in consideration of the role of this neurotransmitter in problem solving and impulse control (Logue and Gould, 2014). Third, because of the focus of our design on probabilistic losses, our design could not incorporate advantageous WPs in our protocol; thus, our current results cannot define whether the observed effects of PPX on probability discounting reflect an actual increase in the propensity for disadvantageous choices or rather a general indifference to probabilistic choices in the task; however, we should note that both conditions are bound to result in an increased engagement in risky choices in relation to disadvantageous options. Fourth, it should be noted that, although our analyses did not reveal any other variations in monoamine levels in RES-treated rats, it is likely that this agent may have induced subtle alterations in the dynamics of corticostriatal release of serotonin or dopamine. These changes (or additional compensatory alterations in other receptors) may participate in PPX-mediated effects by synergizing with the effects of postsynaptic receptors. Finally, although the NAcc has been broadly implicated in the regulation of risk taking and probability discounting, our studies did not include experiments with specific pharmacological targeting of this region (for instance, via local PPX infusions); thus, we cannot rule out that other brain areas may contribute to the effects of PPX on decision-making. These limitations notwithstanding, the present results challenge current interpretations of the neurobiological processes underlying problem gambling and ICDs in PPX-treated patients. As mentioned above, the action of PPX has been posited to reflect an allostatic compensation to the “reward deficiency” secondary to mesolimbic autoreceptor activation (Kapogiannis et al., 2011; Riba et al., 2008). Our findings, however, indicate that PPX may alter probabilistic decision-making by acting directly on post- or extrasynaptic receptors in the NAcc.

Given the serious burden posed by problem gambling and ICDs in PD and RLS patients, it is imperative to decipher the clinical effects of PPX in relation to the specific classes of dopamine receptors. Our results may help elucidate the neurobiological bases of pathological gambling and ICDs induced by dopaminergic agonists, and provide insights into diagnostic approaches to identify patient susceptibility to adverse effects. Furthermore, the current findings may inform future strategies for therapeutic development in problem gambling and ICDs.

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The authors of the present manuscript do not declare any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.neuropharm.2016.11.014.

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