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Dopamine Gene Profiling to Predict Impulse Control and Effects of Dopamine Agonist Ropinirole

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Abstract

■ Dopamine agonists can impair inhibitory control and cause impulse control disorders for those with Parkinson disease (PD), although mechanistically this is not well understood. In this study, we hypothesized that the extent of such drug effects on impulse control is related to specific dopamine gene polymorphisms. This double-blind, placebo-controlled study aimed to examine the effect of single doses of 0.5 and 1.0 mg of the dopamine agonist ropinirole on impulse control in healthy adults of typical age for PD onset. Impulse control was measured by stop signal RT on a response inhibition task and by an index of impulsive decision-making on the Balloon Analogue Risk Task. A dopamine genetic risk score quantified basal dopamine neurotransmission from the influence of five genes: catechol-*O*-methyltransferase, dopamine transporter, and those encoding receptors D1, D2, and D3. With placebo, impulse control was better for the high versus low genetic risk score groups. Ropinirole modulated impulse control in a manner dependent on genetic risk score. For the lower score group, both doses improved response inhibition (decreased stop signal RT) whereas the lower dose reduced impulsiveness in decision-making. Conversely, the higher score group showed a trend for worsened response inhibition on the lower dose whereas both doses increased impulsiveness in decision-making. The implications of the present findings are that genotyping can be used to predict impulse control and whether it will improve or worsen with the administration of dopamine agonists. ■

INTRODUCTION

Impulse control is required to evaluate the potential consequences of a decision, modify behavior, and suppress undesirable actions. Dopamine is necessary for impulse control, whereas dysfunctional levels of frontostriatal dopamine are associated with worse control (Pattij & Vanderschuren, 2008). People with Parkinson disease (PD) are commonly prescribed dopaminergic medication, and 14–20% (Weintraub, Papay, & Siderowf, 2013; Weintraub et al., 2010) develop some form of impulse control disorder (ICD) as a result. It has been suggested that difficulty in performing executive tasks requiring high levels of impulse control may signal an increased risk for the development of ICDs (Poletti & Bonuccelli, 2012). However, the mechanisms of susceptibility to ICD development are not well understood.

One working hypothesis is that ICDs result from a hyperdopaminergic state of the mesocorticolimbic system in early PD, which is then exacerbated by dopaminergic medication. Dopaminergic medications augment depleted nigrostriatal dopamine, but a lack of network specificity consequently increases dopamine within the relatively preserved medial pFC and ventral striatum (Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013; Sawamoto et al., 2008; Cools, 2006). Subsequent dopamine dysregulation within the mesocorticolimbic system may cause deviation from optimal function, adversely influencing motor and cognitive control.

Variation in dopamine-regulating genes can influence impulse control (Nandam et al., 2013; Nemoda, Szekely, & Sasvari-Szekely, 2011) and may affect response to dopaminergic medication. Of particular interest are polymorphisms within genes that affect dopamine neurotransmission such as catechol-*O*-methyltransferase (COMT); dopamine transporter (DAT); and DRD1, DRD2, and DRD3, which regulate the D1, D2, and D3 receptors. D1 and D2 are the most widely expressed dopamine receptors throughout the brain (Nemoda et al., 2011); are central components of motor, cognitive, and limbic cortico-basal ganglia networks (Goto & Grace, 2005; Surmeier, Song, & Yan, 1996; Gerfen et al., 1990); and are specifically implicated in impulse control (Ghahremani et al., 2012; Eagle et al., 2011; Colzato, van den Wildenberg, Van der Does, & Hommel, 2010; Hamidovic, Dlugos, Skol, Palmer, & de Wit, 2009; Comings et al., 1997). D3 receptors are abundant in the mesocorticolimbic system (Gurevich & Joyce, 1999), and the variation within DRD3 has been associated with increased risk of ICDs in PD patients on dopaminergic medication (Lee et al., 2009). The DAT enzyme is predominantly responsible for synaptic dopamine degradation

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within the striatum, whereas COMT is important for dopamine degradation in pFC (Robbins & Arnsten, 2009; Diamond, Briand, Fossella, & Gehlbach, 2004), and both influence impulse control (Congdon, Constable, Lesch, & Canli, 2009; Congdon, Lesch, & Canli, 2008). The combination of polymorphisms across these five genes has bearing on a person's overall level of dopamine neurotransmission. The additive effect of these polymorphisms can be represented as a dopamine gene score and has been shown to predict effects of levodopa on cortical plasticity and motor learning in healthy participants (Pearson-Fuhrhop, Minton, Acevedo, Shahbaba, & Cramer, 2013).

Ropinirole has been associated with ICDs (Weintraub, 2009). It is a non-ergoline D2-like dopamine receptor agonist, showing little or no interaction with nondopaminergic receptors. Like other dopamine agonists, ropinirole mimics the dopamine neurotransmitter and directly activates receptors in the absence of dopamine (Tintner & Jankovic, 2003; Brooks, 2000). The preferential affinity for ropinirole is to activate D3 > D2 > D4 receptors (Coldwell, Boyfield, Brown, Hagan, & Middlemiss, 1999; Perachon, Schwartz, & Sokoloff, 1999) with D3 and D2 being the primary targets. Ropinirole is widely distributed throughout the body and rapidly absorbed after oral administration.

To investigate why ICDs are developed by some people, but not others, we examined how the dopamine agonist ropinirole interacts with dopamine gene polymorphisms to influence impulse control. This study was conducted with healthy adults spanning the typical age of onset for PD. Participants were administered ropinirole or placebo and, 1 hr later, performed computerized tasks to measure impulse control. We hypothesized that impulse control would be modulated by ropinirole and that this would occur in a manner affected by dose and the participant's genetically determined dopamine profile. Specifically, we predicted that ropinirole would improve impulse control in participants with lower basal dopamine neurotransmission, that is, lower dopamine genetic risk scores (GRSs). Conversely, we predicted that ropinirole would worsen impulse control in participants with higher basal dopamine neurotransmission (higher GRS). Global cognitive function was not expected to be affected by ropinirole and served as a control measure.

METHODS

Participants

Healthy adults of typical age for PD onset were screened to determine eligibility for the study. Inclusion criteria were age 40–75 years old, no neurological or cognitive impairment, nonsmoker, normal or corrected-to-normal vision, and no contraindications to ropinirole or domperidone. Potential participants were screened by a neurology registrar (JK) for contraindications. A research nurse (LM) took a single blood sample for genetic analysis. The study was approved by the University of Auckland human participant ethics committee and health and disability Ethics Committee, and written informed consent was obtained from each participant.

Pharmacological Intervention

Participants were orally administered a single dose of placebo, 0.5 or 1.0 mg of the dopamine agonist ropinirole (Janssen-Cilag, Beerse, Belgium) in three experimental sessions with a double-blind, randomized, counterbalanced design. A dose of 1.0 mg was chosen as it is around the commonly prescribed daily therapeutic starting dose for PD (Matheson & Spencer, 2000), and this dose has been tolerated in studies with healthy participants (Monte-Silva et al., 2009; Acton & Broom, 1989). A dose of 0.5 mg was included to investigate the dose dependency of ropinirole effects. Overall, these two doses are low compared with replacement doses for PD. The experimental sessions were spaced at least 1 week apart to prevent cumulative drug effects. To minimize drug-induced systemic side effects of ropinirole, 20 mg of domperidone (Janssen-Cilag, Beerse, Belgium) was administered orally, and participants refrained from caffeine and alcohol on the days of testing.

Experimental Protocol

Before the first experimental session, all participants completed the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996) and Barratt Impulsiveness Scale-II (Patton, Stanford, & Barratt, 1995) tests and were assessed by the research nurse on the motor section of the Unified Parkinson's Disease Rating Scale.

Each experimental session began with administration of domperidone and ropinirole/placebo (after at least an hour of fasting) 1 hr before beginning the computerized impulse control tasks. This timing interval coincides with peak ropinirole blood concentrations (Brefel et al., 1998).

The order of tasks was always anticipatory response inhibition (ARI), Balloon Analogue Risk Task (BART), and Central Nervous Systems Vital Signs (CNSVS) test battery. Collection and analysis of tasks and questionnaires were performed blind to medication (placebo, dose) and genotype.

ARI Task

The ARI task was controlled using custom software written with MATLAB (The MathWorks, Natick, MA), interfaced with two custom-made switches, an A/D USB interface (National Instruments, Austin, TX) and microcontroller (Eleven Freetronics, Victoria, Australia). The goal of the task was to lift the index fingers in time to stop rising indicators at a fixed target on a computer display (Figure 1A). Participants were seated 1 m in front of

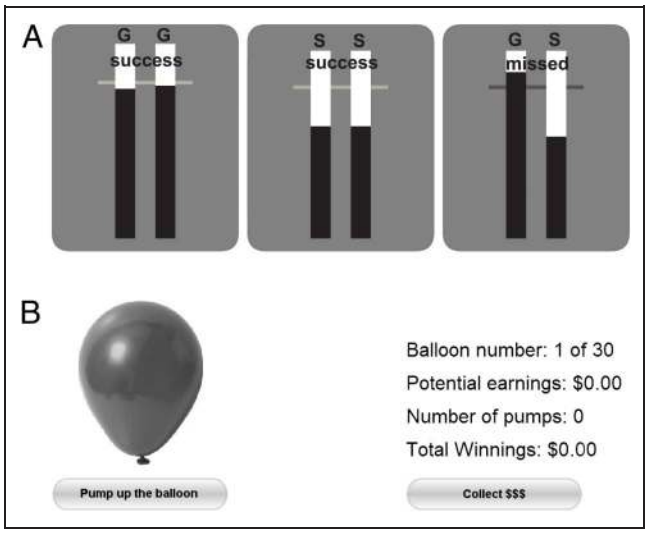

Figure 1. (A) Visual display for the ARI task showing successful Go (GG, left), Stop Both (SS, middle), and Partial trial (Go Left–Stop Right, GS, right). (B) Visual display at the start of BART.

a computer display. Their forearms rested on a table, positioned midway between supination and pronation. The medial aspect of each index finger was used to depress the switches (index finger adduction). Each trial commenced after a variable delay. Both indicators "filled" upward at equal rates, reaching the target line in 800 msec and terminating their rise in 1000 msec, unless stopped prior by releasing either or both switches.

The default response on go trials (GG) required the release of both switches in time to stop the indicators at the target. Only go trials were presented in the first two blocks and as 66% of trials in the remaining eight blocks. Upon trial completion, visual feedback indicated "success" (bars stopped within 30 msec of target) or "miss" to emphasize that trials were to be performed as accurately as possible. The remaining one third of trials were stop trials, where one or both indicators stopped automatically before reaching the target, cueing the participant to inhibit responding with the corresponding digit(s). There were three types of stop trials: stop both (SS), when both indicators stopped automatically, and partial stop trials stop left–go right (SG) and go left–stop right (GS). For each stop trial type, the indicator was initially set to stop at 500 msec. A staircase procedure adjusted the indicator stop time dynamically throughout the task in 25-msec increments to convergence on a 50% success rate.

EMG data were recorded from bilateral first dorsal interosseous (FDI) muscles. Electrodes were placed in a belly tendon montage, and ground electrodes were placed over the posterior surface of the hand. EMG signals were amplified (CED 1902, Cambridge, UK), bandpass filtered (20–1000 Hz), and sampled at 2 kHz (CED 1401, Cambridge, UK). Data were saved for later offline analysis using Signal (CED, Cambridge, UK) and custom software (MATLAB R2012b).

Balloon Analogue Risk Task

The BART was controlled using Inquisit 3 (version 3.0.6.0, Millisecond Software, Seattle, WA). To perform the BART, participants used a mouse to click on an icon that read "Pump up the balloon" to incrementally inflate a red balloon on a laptop screen (Figure 1B). Each press would either (i) incrementally inflate the balloon, causing a visual (and auditory) increase in balloon size, adding 5 cents to the monetary reward, or (ii) burst the balloon (with realistic visual and auditory effect), resulting in no money earned for that balloon. At any time the participant could click a "Collect $$$" icon to end the trial and the current amount would add to their total along with reinforcing auditory feedback. Each balloon was set to explode in a randomly determined manner anywhere from the first pump to filling the entire screen. Participants were told that they would be given a monetary reward equivalent to the final money counter. The balloon (i.e., trial) number, accumulated money for the current balloon, number of pumps for the current balloon, and total winnings thus far were displayed to participants.

Participants completed a single block of 30 trials. The probability of explosion was determined by an array from 1 to 85. Each button press randomly selected a number without replacement. Selection of number one was designated as a balloon explosion. Successive pumps resulted in increasing risk but diminishing returns.

CNSVS Test Battery

The CNSVS consisted of seven tests examining composite memory, verbal memory, visual memory, working memory, processing speed, executive function, RT, complex attention, cognitive flexibility, and sustained attention. The four-part continuous performance test was added to six of the core tests (excluding the finger tapping test). Standardized instructions were given. Test scoring was automated and generated from primary scores based on correct responses, error responses, number of responses, and RTs. Cognitive domain scores were computed as normalized standard scores (mean of 100) representing raw scores relative to age-matched normative data. An overall neurocognitive index (NCI) score was the average of standard scores for composite memory, RT, complex attention, and cognitive flexibility.

Genotyping

DNA was extracted from whole blood samples by salt precipitation. Genotyping for DRD1 rs4532, DRD2 rs1800497, DRD3 rs6280 and COMT rs4680 single-nucleotide polymorphisms (SNPs) was performed using the Agena MassArray iPLEX assay (Agena Bioscience, San Diego, CA). The assay consisted of an initial locus-specific polymerase chain reaction, followed by single base extension using mass-modified dideoxynucleotide terminators of an oligonucleotide

primer (Gabriel, Ziaugra, & Tabbaa, 2009). The four SNPs were included in one multiplex well after accounting for the presence of proximal SNPs. Analysis was performed on the Bruker Mass Spectrometer (Billerica, MA) using parameters optimized for iPLEX chemistry, allowing allele-specific single base extensions to be resolved. The 40 base pair variable number of tandem repeats in the untranslated regulatory region of the DAT gene (rs28363170) underwent polymerase chain reaction with a labeled primer (Mata, Hau, Papassotiropoulos, & Hertwig, 2012) and was assayed separately on a 3130XL genetic analyzer. The results were analyzed using GeneScan (Luxembourg) and PeakScanner (Waltham, MA) software.

A participant's GRS represented the additive effects of the five polymorphisms affecting dopaminergic neurotransmission, as has been described and validated previously in relation to motor learning, Levodopa effects, and cortical plasticity (Pearson-Fuhrhop et al., 2013), and more recently depression (Pearson-Fuhrhop et al., 2014). Each gene was initially equally scored based on the absence (0) or presence (1) of polymorphic alleles that increase dopamine neurotransmission (Table 1). Dopamine GRS could range from 0 (*lowest basal dopamine neurotransmission*) to 5 (*highest neurotransmission*). If an effect of GRS was present, subsequent analyses investigated a weighted GRS generated by substituting each single gene score into the model. We also investigated removing each gene sequentially in order of lowest weighting, to determine their contributions to the composite score (Pearson-Fuhrhop et al., 2013).

Dependent Measures

ARI Task

Lift times (LTs) were determined for successful go (GG) and partial (GS, SG) trials. Average LTs were calculated after removing outliers (±3 *SD*; 1.0 ± 0.1% and 0.2 ± 0.2%, respectively). All LTs are reported in milliseconds relative to the target.

For stop trials, stop signal RT (SSRT), indicator stop time (staircased to 50% success), and percentage of successful trials were determined. SSRT was calculated using the integration method (Verbruggen, Chambers, & Logan, 2013; Logan & Cowan, 1984). SSRT on stop both (SS) trials was the primary dependent measure for this task, as it signifies the efficacy and latency of the inhibitory process in pure response inhibition (RI). Indicator stop time, instead of SSRT, was used as a more direct measure of performance on Partial trials because the calculation of SSRT was not possible in instances where participants couldn't successfully perform these trials.

Balloon Analogue Risk Task

The number of button presses made on trials where a reward was collected ("win") were used to compute the primary measure of interest. The number of button presses on trials when the balloon burst ("loss") were necessarily constrained by software and not used in the analysis. The average number of button presses was calculated for win trials *after* a loss and for win trials *after* a win. For the effect of positive reinforcement, the difference between these two averages was normalized to the mean number of presses after loss trials (the "losses" cancel). The effect of negative reinforcement was normalized to the mean number of presses after win trials (the "wins" cancel). Proportions farther from zero indicate greater behavior modification as a result of reinforcement on a trial-by-trial basis and are indicative of more impulsive decision-making because behavior is too readily modified.

CNSVS Test Battery

The primary dependent measure was NCI. Higher values represent better global cognitive function. Working memory was calculated separately from correct–incorrect responses on the four-part continuous performance test.

Statistical Analysis

LTs were subjected to a repeated-measures ANOVA with a 3 Dose (PLA, ROP 0.5, ROP 1.0) × 2 Digit (Left, Right) × 2 Trial type (Go, Partial) design. All remaining dependent measures were analyzed with a mixed-effects linear regression model in SPSS Statistics (version 21, IBM Corporation, North Castle, NY). Each dependent measure was modeled as a function of Dose (PLA, ROP 0.5, ROP 1.0), GRS, Dose × GRS interaction, and Age. Measures from the CNSVS were standardized scores so Age was removed from the model when predicting these

Table 1. Occurrence of Polymorphisms and Values for GRS

	DRD1 rs4532			*DRD2 rs800497*			*DRD3 rs6280*			*DAT rs28363170*			*COMT rs4680*		
	A/A	*A/G*	*G/G*	*Glu/Glu*	*Glu/Lys*	*Lys/Lys*	*Ser/Ser*	*Ser/Gly*	*Gly/Gly*	*9/9*	*9/10*	*10/10*	*Val/Val*	*Val/Met*	*Met/Met*
Score	0	1	1	1	0	0	0	1	1	1	1	0	0	1	1
Predict freq	0.29	0.50	0.14	0.68	0.29	0.03	0.33	0.49	0.18	0.09	0.42	0.49	0.28	0.50	0.23
Actual freq	0.21	0.64	0.14	0.68	0.29	0.04	0.36	0.43	0.21	0.04	0.54	0.43	0.25	0.54	0.21

DAT 11 alleles scored as 10 alleles. DRD1 = dopamine receptor D1; DRD2 = dopamine receptor D2; DRD3 = dopamine receptor D3; Lys = lysine; Glu = glutamic acid; Ser = serine; Gly = glycine; Val = valine; Met = methionine.

Table 2. Participant Demographics and Clinical Assessment Scores

Age (years)	60 (44–75)
Weight (kg)	73 (52–96)
Sex	15F/13M
Ethnicity	27 White, 1 Maori
BIS-II	59 (38–77)
UPDRS (III)	4 (0–14)
BDI-II	3 (0–15)
MoCA	28 (26–30)

Values are mean (range) unless otherwise noted. BIS = Barratt Impulsiveness Scale (max 120); UPDRS (III) = Unified Parkinson's Disease Rating Scale motor scores (max 56); BDI = Beck Depression Inventory (max 63); MoCA = Montreal Cognitive Assessment (max 30).

dependent variables. A subject-specific random effect factor (μ) accounted for between-subject variation and all other effects ($\beta_0 - \beta_4$) were fixed.

$$y = \beta_0 + \beta_1(\text{Dose}) + \beta_2(\text{GRS}) + \beta_3(\text{Dose} \times \text{GRS}) + \beta_4(\text{Age}) + \mu$$

To explore single-gene relationships, each single-gene score in Table 1 was independently inserted into the model in place of GRS. Model degrees of freedom were calculated using the Satterthwaite method.

Chi-square tests were used to assess Hardy–Weinberg equilibrium for each gene. Missing data were replaced by average of row and column means. The criterion for statistical significance was $\alpha = 0.05$. All results are reported as group means ± *SE*.

RESULTS

Thirty-seven participants were screened, 33 recruited, and 30 completed all experimental sessions. Two withdrew due to drug-induced side effects (nausea: 1, dizziness: 1) and one due to scheduling problems. Generally, the medications were tolerated with the following exceptions for ropinirole (nausea: 2, vomiting: 1, drowsiness: 5) and domperidone (dry mouth: 1, headache: 1). Two participants were unable to adhere to one or more protocols. Results are reported for the remaining 28 participants. Demographic details and clinical assessment scores are presented in Table 2; *F* statistics, *p* values, and η_p^2 effect sizes are reported for the mixed-effects linear regression models in Tables 3 and 4. All genes were in Hardy–Weinberg equilibrium ($.12 < p < .89$, Table 1). The distribution of dopamine GRS is shown in Figure 2A. Scores of 2 and 3 were grouped (Low, $n = 12$; age = 44–73 years) as were scores of 4 and 5 (High, $n = 16$; age = 44–75 years). No participant had the rare GRS of 0 or 1.

ARI Task

Go Trials

Go trials were completed successfully with LTs occurring 32 ± 2 msec after the target as is typical for older adults with this task (Coxon, Van Impe, Wenderoth, & Swinnen, 2012). There was a main effect of Trial type ($F(1, 26) = 127.9$, $p < .001$) with LTs delayed to an average of 96 ± 6 msec after the target on Partial trials. There was a main effect of Digit ($F(1, 26) = 6.4$, $p = .018$) with right LT faster than left LT when collapsed across Trial type and Dose (57 ± 5 msec vs 70 ± 3 msec). There was no effect of Dose ($F(1, 26) = 0.6$, $p = .557$) or any interactions (all ps $> .218$).

Stop Both Trials

Stop both trials were performed as expected with a success rate just above 50% (58.6 ± 1.8%). The model predicted that SSRT for SS trials was dependent on Dose ($p = .025$), the Dose × GRS interaction ($p = .029$, Table 3), and the intercept ($\beta_0 = 243$ msec, $t(27) = 7.2$, $p < .001$). Predicted SSRT decreased by 66 msec with 0.5 mg ROP ($t(27) = -2.6$, $p = .013$) and by 61 msec with 1.0 mg ROP ($t(27) = -2.4$, $p = .021$). The pattern of interaction results for predicted SSRT is evident in the sample data (Figure 2B). Post hoc tests revealed that participants with a low GRS had longer SSRTs at baseline (236 ± 10 msec) than those with high scores (199 ± 7 msec, unpaired *t* test: $t(26) = 3.0$, $p = .008$). SSRT decreased with ROP for low GRS (paired *t* tests: 0.5 mg, 211 ± 9 msec, $t(11) = -2.8$, $p = .008$; 1.0 mg, 214 ± 9 msec, $t(11) = -2.2$, $p = .025$) but tended to increase with ROP for high scores, especially at the lower dose (paired *t* tests: 0.5 mg, 213 ± 6 msec, $t(15) = 1.5$, $p = .072$; 1.0 mg, 205 ± 8 msec, $t(15) = 0.6$, $p = .280$).

Entered into the model separately, no single gene significantly interacted with ROP to predict SSRT (Dose × Gene interactions: $.06 < p < .64$). DRD3 had the highest weighting (0.32), then DAT (0.25), DRD1 (0.22), COMT (0.14), DRD2 (0.08). The Weighted GRS produced very similar results with a fixed effect of Dose ($p = .010$) and Dose × Weighted GRS interaction ($p = .012$). Removing the lowest-weighted gene DRD2 from the Weighted GRS had a negligible effect on the Dose × Weighted GRS interaction ($p = .011$). Removing COMT weakened the interaction ($p = .029$) and removing DRD1 produced no Dose × Weighted GRS interaction ($p = .159$). At least four genes were necessary to explain the Dose × GRS interaction for ARI task (SSRT) performance.

Partial Stop Trials

On average, partial stop trials were more difficult than stop both trials, with success rates just below 50% (SG, 41.8 ± 3.3%; GS, 36.4 ± 3.8%). Eleven participants were unable to complete any successful trials for at least one

Table 3. Main Effects from Mixed-effects Linear Regression Models

		Unweighted				*Weighted*			
Dependent Measure	*Model Term*	*F*	*df*	*p*	η^2_p	*F*	*df*	*p*	η^2_p
SSRT	Dose	4.0	2.51	**.025**	**0.14**	5.0	2.51	**.010**	**0.16**
	GRS	1.6	1.30	.211	0.05	1.3	1.30	.271	0.04
	Age	1.8	1.30	.187	0.05	1.5	1.30	.230	0.05
	Dose × GRS	3.8	2.51	**.029**	**0.13**	4.8	2.51	**.012**	**0.16**
Positive reinforcement	Dose	2.5	2.54	.091	0.08	3.5	2.54	**.037**	**0.11**
	GRS	0.2	1.31	.639	0.00	0.3	1.31	.585	0.01
	Age	0.0	1.31	.904	0.00	0.0	1.31	.882	0.00
	Dose × GRS	2.3	2.54	.107	0.08	4.4	2.54	**.017**	**0.14**
Negative reinforcement	Dose	4.0	2.54	**.024**	**0.13**	5.4	2.53	**.008**	**0.17**
	GRS	0.2	1.32	.668	0.01	0.2	1.31	.699	0.01
	Age	0.0	1.32	.862	0.00	0.0	1.31	.895	0.00
	Dose × GRS	3.7	2.54	**.031**	**0.12**	6.4	2.53	**.003**	**0.19**
NCI	Dose	0.5	2.48	.636	0.02				
	GRS	5.9	1.27	**.022**	**0.18**				
	Dose × GRS	0.3	2.48	.711	0.01				
Working memory	Dose	2.7	2.48	.080	0.10				
	GRS	3.7	1.26	.066	0.12				
	Dose × GRS	2.5	2.48	.089	0.09				

Bold indicates $p > 05$.

Partial trial type in at least one session, even with the staircase procedure. Two participants were unable to perform any SG trials successfully ($n = 26$) and one could not perform GS trials successfully ($n = 27$).

The indicator stop time on GS and SG trials was dependent on the intercept ($t(26) = 4.3$, $p < .001$ and $t(25) = 5.9$, $p < .001$, respectively) but was not dependent on Dose, GRS, or a Dose × GRS interaction (all ps $> .179$). Partial GS trials only showed a fixed effect of Age ($p < .001$). With each year increase in age, there was a 9-msec increase in the predicted indicator stop time relative to target.

Table 4. Main Effects in Balloon Analogue Risk Task Using DAT Score

Dependent Measure	*Model Term*	*F*	*df*	*p*	η^2_p
Positive reinforcement	Dose	3.0	2.55	.059	0.10
	DAT	1.7	1.32	.205	0.05
	Age	0.0	1.32	.915	0.00
	Dose × DAT	5.6	2.55	**.006**	**0.17**
Negative reinforcement	Dose	4.2	2.54	**.021**	**0.13**
	DAT	1.1	1.31	.313	0.03
	Age	0.0	1.31	.862	0.00
	Dose × DAT	6.9	2.54	**.002**	**0.20**

Bold indicates $p > 05$.

Balloon Analogue Risk Task

Using the unweighted GRS to predict effect of negative reinforcement, there was a fixed effect of Dose ($p = .024$) with the predicted number of presses after loss trials decreasing less with 0.5 mg ROP ($t(27) = -2.3$, $p = .027$) than PLA, with no difference between 1.0 mg ROP and PLA ($t(27) = 0.3$, $p = .786$, Table 3). There was a Dose × GRS interaction ($p = .031$; Figure 2D). Participants with a low GRS made fewer impulsive decisions on 0.5 mg ROP (PLA: 0.10 ± 0.05; ROP: 0.02 ± 0.05) whereas those with a high GRS made more (PLA: 0.05 ± 0.05; ROP: 0.12 ± 0.05), although these differences did not reach significance in post hoc testing ($p > .17$). A similar pattern of means were observed for positive reinforcement (Figure 2C), but with no fixed effect of Dose ($p = .091$) or Dose × GRS interaction ($p = .107$, Table 3).

Entered into the model separately, the DAT polymorphism interacted with ROP to predict an effect of both

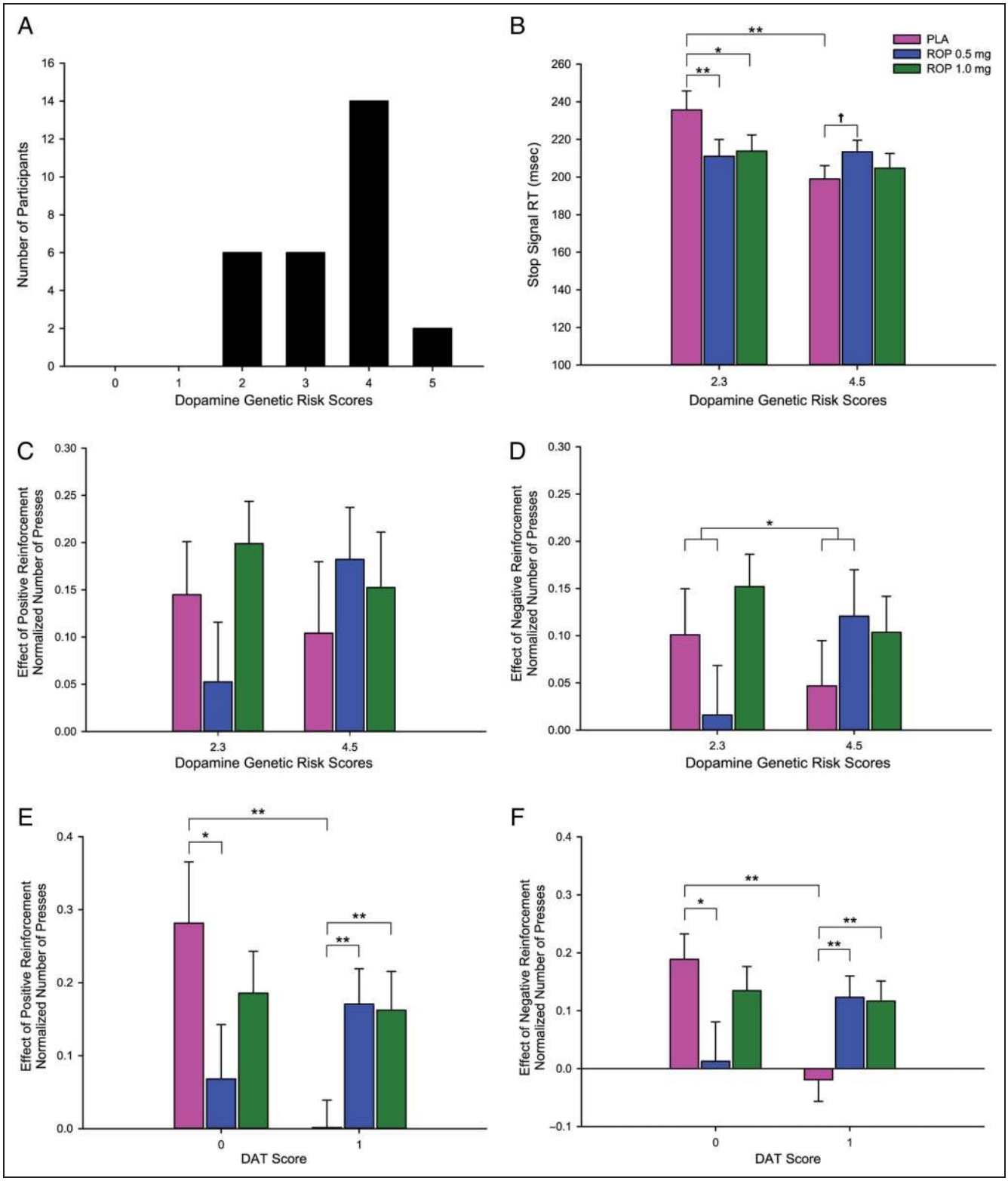

Figure 2. (A) Distribution of GRSs. SSRTs (B) and impulsive decision-making (C–F) for low versus high neurotransmission. PLA = placebo; ROP = ropinirole. $^{\dagger}p = .072$. $^{*}p < .05$. $^{**}p < .01$.

negative (Dose × DAT Score interaction: $p = .002$; Figure 2F) and positive reinforcement (Dose × DAT Score interaction: $p = .006$; Figure 2E; Table 4). No other gene could predict this interaction (Dose × Gene interactions: $.27 < p < .96$). At baseline, participants with a DAT score of 0 (DAT_0, lower dopamine neurotransmission, $n = 12$) made more impulsive decisions than DAT_1 participants (higher dopamine transmission, $n = 16$)

after negative (DAT_0: 0.19 ± 0.04; DAT_1: 0.02 ± 0.04, unpaired t test: $t(26) = 3.6, p = .001$) and positive reinforcement (DAT_0: 0.28 ± 0.08; DAT_1: 0.00 ± 0.04, unpaired t test: $t(26) = 3.0, p = .008$). DAT_0 participants *reduced* impulsivity with 0.5 mg ROP (paired t tests: both reinforcement $t(11) > -1.9$, $p < .044$) but not 1.0 mg ROP (paired t tests: both $p > .176$). Conversely, DAT_1 participants *increased* impulsivity with 0.5 mg (paired t tests: both reinforcement $t(15) > 2.6$, $p < .009$) and 1.0 mg ROP (paired t tests: both $t(15) > 3.7$, $p < .002$).

DAT had the highest weighting (0.60) in the Weighted GRS, then DRD2 (0.24), DRD3 (0.08), COMT (0.05), DRD1 (0.03). The Weighted GRS produced a fixed effect of Dose ($p = .037$) and Dose × Weighted GRS interaction ($p = .017$) for positive reinforcement and the effect of Dose ($p = .008$) and Dose × Weighted GRS interaction ($p = .003$) for negative reinforcement (Table 3). Removing the lowest weighted genes in order (DRD1, COMT, DRD3) had a negligible effect on the Dose × Weighted GRS interaction for negative (all ps $< .004$) and positive reinforcement (all ps $> .015$). Therefore, the DAT polymorphism alone accounted for the Dose × GRS interaction for BART performance.

CNSVS Test Battery

The predicted NCI score was not dependent on Dose or a Dose × GRS interaction (Table 3). There was a significant intercept ($\beta_0 = 112$, $t(27) = 18.6$, $p < .001$) and a fixed effect of GRS ($p = .022$). However, there was no systematic increase or decrease in NCI as a function of GRS ($t(27) = -1.5$, $p = .130$), and post hoc tests indicated no difference in NCI between GRS. Predicted working memory was not dependent on Dose, GRS, or a Dose × GRS interaction (all ps $> .065$; Table 3), only the intercept ($\beta_0 = 115$, $t(27) = 9.1$, $p < .001$).

DISCUSSION

This study produced several novel findings. Impulse control of healthy adults differed between those with high and low levels of basal dopamine neurotransmission, as determined by a dopamine GRS. A single administration of ropinirole interacted with genetic variations in dopamine transmission to affect impulse control in predictable ways. In support of our hypothesis, RI improved for those with a lower GRS when given a single dose of ropinirole and tended to worsen for those with higher scores. Whereas a polygenic risk score was necessary to account for SSRT during RI, the DAT polymorphism alone determined impulsive decision-making during the BART. Ropinirole decreased impulsive decision-making for those with the lower DAT score and increased it for those with the higher DAT score. Ropinirole had no effect on global cognitive function so the results appear to be specific to impulse control.

Consistent with previous studies, we propose an inverted-U relationship between dopamine levels and impulse control (Farrell, Tunbridge, Braeutigam, & Harrison, 2012; Congdon et al., 2009). Figure 3 illustrates how the GRS may determine a person's starting position on the curve. People with higher scores have closer to optimal levels of dopamine for RI, whereas people with lower scores may sit lower on the curve. In this study, this was verified by faster SSRTs for participants with a higher GRS. Adults with more optimal levels of dopamine neurotransmission also demonstrate greater neural activation within the RI network (Congdon et al., 2009). Interestingly, Congdon and colleagues did not find an effect on SSRT when contrasting polymorphisms within COMT and DAT individually. Variation in DRD2 expression alone can modulate RI (Ghahremani et al., 2012; Colzato et al., 2010; Hamidovic et al., 2009). The current study extends these findings by quantifying the influence of a greater range of polymorphisms that influence dopamine neurotransmission and demonstrating that a dopamine GRS can be used to predict baseline measures of RI.

A single administration of ropinirole temporarily shifted participants rightward along the inverted-U curve either toward or beyond optimal dopamine concentrations for RI (Figure 3). Both doses of ropinirole shifted participants with a lower GRS toward optimal levels, as evident by improved SSRTs. For participants with a higher GRS, basal dopamine may have been closer to optimal levels. In this case, 0.5 mg ropinirole caused a nonsignificant worsening of SSRT ($p = .072$). Combined, these results indicate that there was no dose-dependent effect of ropinrole on RI, perhaps because of the low dosages of ropinirole used in this study. The absence of dose

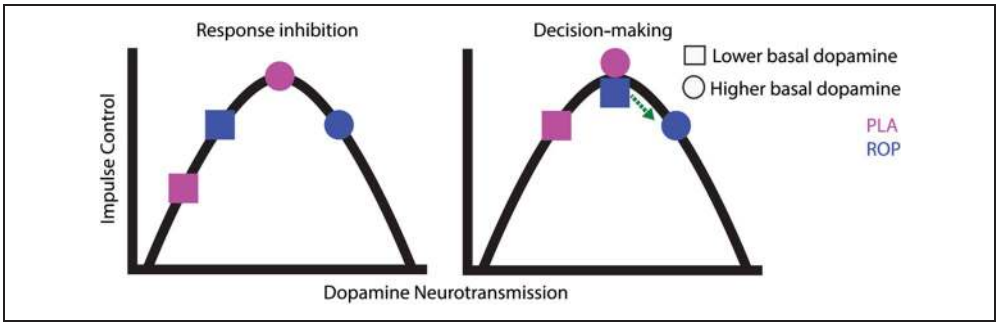

Figure 3. Relationship between dopamine neurotransmission and RI (left) and decision-making (right). Squares: GRSs 2, 3 for RI, DAT_0 for decision-making; circles: GRSs 4, 5 for RI, DAT_1 for decision-making. PLA = placebo; ROP = 0.5 mg ropinirole.

dependency may also be due to only two participants being at the highest range of basal neurotransmission (GRS of 5). Previously, a single administration of up to 1.0 mg ropinirole (Monte-Silva et al., 2009) and 0.5 mg pramipexole (Pizzagalli et al., 2008) was shown to influence plasticity and reinforcement learning in healthy participants, respectively. Consistent with these findings, the divergent effect of ropinirole on RI in this study was evident during peak dopamine agonist concentrations.

The current study extends the use of a dopamine polygenic score into the context of impulse control. Variation within DRD3 has been associated with increased risk of ICDs in PD patients on dopaminergic medication (Lee et al., 2009), and the D3 receptor is a target of ropinirole (Matheson & Spencer, 2000). The present results indicate that DRD3 was weighted most heavily to predict the interaction between GRS and ropinirole on SSRT. However, variation in DRD3 alone could not account for the effects of ropinirole. RI might better be predicted by quantifying widespread dopaminergic neurotransmission rather than DRD3 alone, because of the differential expression of dopamine genes across the network of brain regions implicated in RI. This includes frontal cortical regions (e.g., right inferior frontal gyrus) in which COMT has a larger impact on dopamine neurotransmission. A four-gene score that omits DRD2 may be sufficient to capture the effect of ropinirole on RI and warrants further investigation. However, a strength of the five-gene score is that it was an a priori, hypothesis-driven score based on previously published literature (Pearson-Fuhrhop et al., 2013, 2014). The ARI task might be clinically useful in the context of ICDs. Baseline measures of SSRT and dopamine GRS indicate a person's starting position on the inverted-U curve and, combined, may identify those at risk of developing ICDs when taking dopamine agonists.

Surprisingly, the DAT polymorphism alone predicted impulsive decision-making. The DAT protein is involved in synaptic dopamine degradation and is particularly important in the striatum. Lower DAT activity results in less reuptake of synaptic dopamine and consequently higher levels of dopamine neurotransmission (VanNess, Owens, & Kilts, 2005; Heinz et al., 2000). DAT_1 participants (DAT score = 1) had higher basal levels of striatal dopamine neurotransmission and better impulse control than DAT_0 participants. Those with DAT_1 made fewer impulsive decisions on placebo after both positive and negative reinforcement. This is consistent with individual differences in general risk taking on the BART, with lower DAT activity being associated with less risky behavior (Mata et al., 2012). Mata and colleagues inferred risk taking from average total number of button presses on collected trials. This study quantified behavioral modification on a trial-by-trial basis as a result of rewards and losses to assess impulsive decision-making (Ashenhurst, Bujarski, Jentsch, & Ray, 2014) and extend the findings of Mata and colleagues to show how DAT polymorphism dictates impulsive decision-making.

The DAT protein influences basal dopamine neurotransmission and tonic dopamine activity within the dorsal and ventral striatum. Striatal dopamine is associated with reinforcement learning from positive and negative outcomes (Cox et al., 2015; Frank, Moustafa, Haughey, Curran, & Hutchison, 2007). Increasing tonic dopamine activity in the ventral striatum beyond optimal levels disrupts behavior modification (Goto & Grace, 2005; Schultz, 2002). In this study, ropinirole interacted with the DAT polymorphism in a predictable way. This can be likened to shifting a participant rightward along an inverted-U curve either toward optimal levels of striatal dopamine neurotransmission (DAT_0) or beyond them (DAT_1). Figure 3 depicts the working hypothesis (green arrow) that 1.0 mg ropinirole degrades decision-making in people with lower striatal dopamine neurotransmission, perhaps because striatal dopamine levels were near optimal at 0.5 mg. This may explain why 0.5 mg ropinirole improved decision-making whereas 1.0 mg degraded it. When combined with DAT genotyping, the BART may assist in identifying people who may be more susceptible to developing a hyperdopaminergic state of the ventral striatum when given dopamine agonist medication.

Performance on the bimanual ARI task was as expected for healthy older adults. Go LTs were typical for this age range (Coxon et al., 2012), occurring later than for younger adults performing an identical task (MacDonald, Stinear, & Byblow, 2012). As expected, LTs on Partial trials were delayed (MacDonald, Coxon, Stinear, & Byblow, 2014; MacDonald et al., 2012; Coxon, Stinear, & Byblow, 2007, 2009). Furthermore, partial cancellation on GS trials was more difficult with increasing age (Coxon et al., 2012, 2014). In contrast to SSRT obtained from Stop Both trials, performance on Partial trials was not influenced by GRS or ropinirole dosage. Compared with simple RI, partial movement cancellation involves more complex neural mechanisms as the noncued movement component still needs to be executed. The delay in the executed component may reflect processes of inhibition, reprogramming, and initiation (MacDonald et al., 2014; Coxon et al., 2007, 2009). Partial trials may therefore engage mechanisms beyond pure impulse control as opposed to SSRT from Stop Both trials, and this may explain the differential sensitivity to dopaminergic factors between these two trial types.

The sample size obtained within the recruitment period was less than anticipated and is a limitation in this study. Our target sample size was 50 based on the study by Pearson-Fuhrhop et al. (2013). Our smaller sample did not capture the full range of dopamine GRSs, particularly scores of 0 or 1. We are therefore not able to comment on the effect of GRSs 0 and 1 in the context of impulse control and ropinirole, limiting the comparison between our study and the ones by Pearson-Fuhrhop et al. (2013, 2014). Sample size also necessitated limiting the number of predictors in the model. For example, weight was not included to avoid overparameterization. However, this was

not considered to have a major impact on our results as shown previously for gene score predictions of motor learning (Pearson-Fuhrhop et al., 2013). It is not currently known whether or not the present results are specific to ropinirole because no other dopaminergic medications were investigated in this study.

In summary, the effect of ropinirole on impulse control can be conceptualized as shifting people rightward along an inverted-U curve to their benefit or detriment. The net result from the rightward shift depends on basal levels of dopamine neurotransmission, which are significantly influenced by genetic factors. Genetic variation in dopamine neurotransmission may have only modest behavioral consequences for healthy individuals; however, there may be more serious implications for those prescribed large doses of dopaminergic medications over a longer time period, as is common for the treatment of PD. This study provides preliminary evidence that dopaminergic genotyping combined with baseline measures of RI and impulsive decision-making may be useful for identifying people at risk of developing ICDs on dopamine agonists. It remains to be determined if such an approach could lead to better individualized treatments for PD.

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