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Motor Impulsivity in Parkinson Disease: Associations with COMT and DRD2 polymorphisms

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Abstract

Parkinson disease (PD) is an age-related degenerative disease of the brain, characterized by motor, cognitive, and psychiatric symptoms. Neurologists and neuroscientists now understand that several symptoms of the disease, including hallucinations and impulse control behaviors, stem from the dopaminergic medications used to control the motor aspects of PD. Converging evidence from animals and humans suggests that individual differences in the genes that affect the dopamine system influence the response of PD patients to dopaminergic medication. In this study, we tested the hypothesis that patients taking dopamine replacement therapy who carry candidate alleles that increase dopamine signaling exhibit greater amounts of motor impulsivity. We examined the relation between inhibitory ability (measured by the Stop Signal Task) and polymorphisms of COMT Val158Met and DRD2 C957T in patients with idiopathic PD. On the Stop Signal Task, carriers of COMT Val/Met and Met/Met genotypes were more impulsive than Val/Val carriers, but we did not find a link between DRD2 polymorphisms and inhibitory ability. These results support

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the hypothesis that the Met allele of COMT confers an increased risk for behavioral impulsivity in PD patients, whereas DRD2 polymorphisms appear to be less important in determining whether PD patients exhibit a dopamine overdose in the form of motor impulsivity.

Keywords

Parkinson disease; impulse control disorder; dopamine; COMT

Parkinson disease (PD) is an age-related neurodegenerative disorder commonly characterized by resting tremor, rigidity, slowness of movement, and postural instability (Shulman, De Jager, & Feany, 2011). In addition, we now know that the extrapyramidal signs are accompanied by a broad range of nonmotor symptoms (Brooks & Pavese, 2010; Growdon, Corkin & Rosen, 1990; Kensinger, Shearer, Locascio, Growdon, & Corkin, 2003; Locascio, Corkin, & Growdon, 2003). The cognitive sequelae include visuospatial deficits and difficulty performing tasks that require cognitive control, while psychiatric disorders consist of anxiety, depression, impulsive behaviors, insomnia, and hallucinations (Owen, 2004; Voon, Mehta, & Hallett, 2011; Weintraub, Comella, & Horn, 2008). These nonmotor symptoms negatively impact patients' quality of life, and typically do not respond to, or are worsened by, the medications used to treat the motor symptoms (Weintraub, Comella, & Horn, 2008).

Neuropathology of PD

The cardinal motor features of PD are typically attributed to a loss of dopaminergic neurons in the substantia nigra that project from the midbrain to the striatum (Fearnley & Lees, 1991; Jellinger, 2004). While denervation of dopaminergic nigrostriatal projections may explain the primary motor symptoms of PD, abnormalities are also seen in non-dopaminergic nuclei (Calabresi, Picconi, Parnetti, & Di Filippo, 2006; Dubois, Pilon, Lhermitte, & Agid, 1990; Pillon et al., 1989; Rye & DeLong, 2003). Notably, degeneration of the cholinergic basal forebrain (Calabresi, et al., 2006; Javoy-Agid et al., 1981; Ziegler et al., 2013) and noradrenergic locus coeruleus (Zarow, Lyness, Mortimer, & Chui, 2003; Zweig, Cardillo, Cohen, Giere, & Hedreen, 1993) probably contributes to the nonmotor deficits (Brooks & Pavese, 2010). Indeed, a prominent hypothesis regarding the neuropathological progression of PD posits that Lewy body deposition commences in the enteric and peripheral nervous system, prior to appearing in the brainstem, and then progresses rostrally to the midbrain, forebrain, and neocortex (Braak et al., 2003; Halliday, McCann, & Shepherd, 2012).

In the dopaminergic midbrain, the ventrolateral tier of the substantia nigra pars compacta (SNpc) is initially targeted, followed by the dorsolateral tier of the SNpc, while the ventral tegmental area (VTA) is relatively spared until the latest stages of the disease (Fearnley & Lees, 1991). This pattern of cell loss in the early stages causes severe dopamine depletion in the dorsal striatum and moderate depletion in the ventral striatum, while relatively sparing dopaminergic function in the ventral striatum (Damier, Hirsch, Agid, & Graybiel, 1999; Kish, Shannak, & Hornykiewicz, 1988). Regions within the striatum are differentially connected with specific areas of the cortex by functionally distinct cortico-striatal loops, (Alexander, DeLong, & Strick, 1986; Haber & Knutson, 2010); dopamine depletion in the

dorsal striatum alters the motor—loop function, leading to the motor symptoms of PD. Treatment with the dopamine precursor levodopa or dopamine agonists is the gold standard for reducing the motor symptoms. These drugs are believed to work by increasing dopaminergic transmission in the motor loop of the striatum (Cools, 2006). Use of levodopa or dopamine agonists, however, sometimes causes psychiatric side effects, including impulse control behaviors (Antonelli et al., 2013; Claassen, Kanoff, & Wylie, 2013), possibly due to overstimulation of the relatively preserved ventral cortico-striatal loops (Cools, 2006).

Impulse control behaviors

Impulsive behaviors in PD include pathologic gambling, binge eating, hypersexuality, and excessive shopping (Djamshidian, Cardoso, Grosset, Bowden-Jones, & Lees, 2011; Klos, Bower, Josephs, Matsumoto, & Ahlskog, 2005; Nirenberg & Waters, 2006; Voon et al., 2007; Weintraub et al., 2006). To date, impulsivity in PD has been studied predominantly using clinical interviews or self-report questionnaires (Bentivoglio, Baldoner, Ricciardi, De Nigris, & Daniele, 2013; Eysenck & Eysenck, 1978; Patton, Stanford, & Barratt, 1995). Although information gained from such reports is valuable, these measures are often relatively nonspecific. Impulse control behaviors typically start, with variable onset times, after the introduction of dopaminergic medications or after a dose increase (Gallagher, O'Sullivan, Evans, Lees, & Schrag, 2007). They often remit when medication is decreased or discontinued and are less frequently associated with deep brain stimulation (Djamshidian et al., 2013). All dopaminergic medications (levodopa, dopamine agonists) can induce psychiatric side effects, but agonists are more likely to do so than levodopa (Gallagher, et al., 2007; Voon, Hassan, Zurowski, Duff-Canning et al., 2006).

While dopamine replacement therapy improves motor function in PD by increasing signaling in the dopamine-depleted cortico-striatal motor loop, it can have beneficial and deleterious effects on cognitive functions subserved by the associative and limbic loops, respectively (Cools, 2006; Dagher & Robbins, 2009). The idea that dopamine replacement therapy exerts opposing impacts on functions that engage these two loops is embodied in the dopamine overdose hypothesis (Cools, 2006). Although this view provides an explanation for the interaction between medication status and cognitive performance at a group level, it cannot account for individual variability in cognitive performance. The dopamine overdose hypothesis does not explain why some patients taking dopamine replacement therapy do not develop the side effects, and why the levodopa daily dose and levodopa-equivalent daily dose (LEDD) are similar for affected and unaffected patients (Gallagher, et al., 2007; Papapetropoulos & Mash, 2005; Voon, Hassan, Zurowski, Duff-Canning, et al., 2006). In addressing these issues, we proposed that genetic variation plays a role in the pathogenesis of the medication-induced alterations in behavior.

Genetics of response to dopaminergic medication

Research into the genetic causes of individual variability in impulsivity has implicated polymorphisms in the catechol-O-methyltransferase (*COMT*), D₂ receptor (*DRD2*), D₃ receptor (*DRD3*), and D₄ receptor (*DRD4*) genes (Boettiger et al., 2007; Congdon, Lesch, & Canli, 2008; Eisenberg et al., 2007; Retz, Rosler, Supprian, Retz-Junginger, & Thome, 2003;

Thompson et al., 1997). In healthy adults, increased risk for impulsivity is linked with allelic forms that either a) reduce synaptic levels of dopamine (e.g., at least one *COMT* Val allele) (Boettiger et al., 2007; Chen et al., 2004), b) reduce receptor binding affinity for dopamine (e.g., having at least one *DRD2* 957C allele, having at least one *ANKK1* TaqI A1 allele, or having at least one *DRD3* Ser allele) (Retz, et al., 2003), or c) reduce receptor coupling efficacy to second messenger proteins (e.g., presence of the *D_{4.7}* allele) (Congdon, et al., 2008). In short, healthy adults with reduced dopamine signaling, conferred by the presence of one or more of the alleles noted above, show increased impulsivity. Because *COMT* and *DRD2-4* genes encode proteins that directly interact with anti-Parkinsonian medications, we reasoned that polymorphisms that increase dopamine signaling may underlie the psychiatric side effects of dopamine replacement therapy in PD.

Pharmacology and genetics of response inhibition

Much of the behavioral research on the neural and chemical underpinnings of impulsivity has focused on response inhibition, the ability to inhibit a prepotent motor response, and several experiments have documented reduced inhibitory ability in PD patients. In a Go/NoGo task, patients responded more often than controls on trials when they should not have responded (NoGo trials) (Cooper, Sagar, Tidswell, & Jordan, 1994). Similarly, reaction times in the Stop-Signal Task were significantly longer in PD patients than in matched controls (Gauggel, Rieger, & Feghoff, 2004), and this reduced inhibitory ability in PD was independent of general slowing and cognitive impairment (Gauggel, et al., 2004), indicating a selective deficit in inhibitory ability.

Pharmacological studies in animals suggest that dopamine plays a critical role in modulating response inhibition: D-amphetamine, cocaine, and the dopamine reuptake inhibitor GBR 12909, all of which boost dopaminergic neurotransmission, decreased response inhibition in rats, measured by the number of premature responses in the 5-Choice Serial Reaction Time Task (Cole & Robbins, 1987; van Gaalen, Brueggeman, Bronius, Schoffelmeer, & Vanderschuren, 2006). On this task, a dopamine antagonist blocked the impulsivity induced by an intra-accumbens injection of d-amphetamine (Cole & Robbins, 1987). Further, methylphenidate, which increases synaptic levels of dopamine, reduced inhibitory deficits in children and adults diagnosed with ADHD (Aron, Dowson, Sahakian, & Robbins, 2003; Bedard et al., 2003). The pharmacological alteration of response inhibition appears to be baseline-dependent, with improved inhibitory ability limited to individuals with low performance at baseline (Boonstra, Kooij, Oosterlaan, Sergeant, & Buitelaar, 2005; Perry, Stairs, & Bardo, 2008). This result is consistent with the inverted-U dopamine response hypothesis whereby only individuals on the left-leg of the inverted-U curve (i.e., those with reduced dopamine signaling) improve when receiving dopaminergic medication.

Genetic research also supports a role for dopamine in inhibitory control. A PET study showed that the number of *D₂/D₃* receptors was lower in impulsive compared to non-impulsive rats (Dalley et al., 2007). Healthy adults with at least one 7-repeat allele of *D₄*, which reduces dopamine signaling, had longer Stop-Signal reaction times (SSRT) compared to individuals without the 7-repeat allele (Congdon, et al., 2008), and children with ADHD who carried the 7-repeat allele of *D₄* required higher doses of methylphenidate for symptom

improvement (Hamarman, Fossella, Ulger, Brimacombe, & Dermody, 2004). Healthy adults with at least one Met allele of *COMT* showed greater SSRT-related brain activation in the right inferior PFC than those with the Val/Val genotype (Congdon, Constable, Lesch, & Canli, 2009), suggesting better inhibitory control in the former group (Aron & Poldrack, 2006; Congdon, et al., 2009).

In summary, converging evidence from studies in animals, healthy humans, and humans with ADHD suggest that dopamine-induced changes in inhibitory ability follow an inverted-U curve, and that performance is modulated by natural variation in genes that regulate the level of dopamine signaling. Building on prior work, we predicted that variations in *COMT* and *DRD2-4* would alter inhibitory ability in PD patients receiving dopamine replacement therapy. Two lines of evidence support this hypothesis: first, the baseline-dependent influence of medication on impulsivity, and second, the relation between genetic variation in the dopamine-system and activation in the network mediating response inhibition. We hypothesized that patients who carry genotypes that increase dopamine signaling are more likely to experience deficits in response inhibition due to dopamine overdose.

Materials and methods

Participants

We recruited 123 patients with idiopathic PD from the Movement Disorders Units at the Massachusetts General Hospital and Brigham and Women's Hospital (Table 1). The inclusion criteria were: idiopathic PD according to the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria (Hughes, Daniel, Kilford, & Lees, 1992); mild to moderate disease indicated by Hoehn and Yahr (H&Y) stages I-III; taking dopamine replacement therapy; no significant cognitive deficits, indicated by the Mini-Mental State Examination (MMSE) score ≥ 26 (Folstein, Folstein, & McHugh, 1975); at least 12 years of schooling; and ability to give informed consent. The exclusion criteria were: history of a brain disorder other than PD; serious medical conditions (e.g., cancer, diabetes, heart disease); and severe depression indicated by a Beck Depression Inventory (BDI) score ≥ 18 (Beck, Steer, Ball, & Ranieri, 1996). All participants gave written informed consent using procedures approved by the MIT Committee on the Use of Humans as Experimental Subjects and by the Partners Human Research Committee.

Participants were taking their usual dose of dopaminergic medications and were optimally medicated during testing. The self-identified racial and ethnic distribution of participants was: 122 White/not Hispanic or Latino and 1 Asian. To compare dopaminergic medication among patients, each participant's dopaminergic drug regimen was converted to a levodopa equivalent daily dose (LEDD) according to a published formula: $LEDD = \text{levodopa/carbidopa regular (mg)} + \text{levodopa/carbidopa CR (mg)} \times 0.75 + [\text{levodopa/carbidopa (mg)} + \text{levodopa/carbidopa CR (mg)} \times 0.75] \times 0.33$ if on entacapone or tolcapone + $[\text{levodopa/carbidopa (mg)} + \text{levodopa/carbidopa CR (mg)} \times 0.75] \times 1.2$ if on 10 mg selegiline ($\times 1.1$ if on 5 mg selegiline) + $\text{bromocriptine (mg)} \times 10 + \text{pramipexole (mg)} \times 67 + \text{requip (mg)} \times 20 + \text{pergolide (mg)} \times 100$ (Katzenschlager et al., 2008; V. Voon, Hassan, Zurowski, de Souza et al., 2006).

Experimental Design

Participants performed a version of the Stop-Signal Task. Stimuli were presented using the Matlab Psychophysics Toolbox (Brainard, 1997) on a Dell desktop computer (3.2 GHz; 1GB RAM) running Windows XP with a Viewsonic P220F 22-inch CRT monitor. On each trial, a left- or right-pointing green arrow appeared on a black computer screen (Figure 1). For Go trials, participants indicated the direction of this arrow by pressing the left or right arrow key on the keyboard as fast as possible, using their preferred index and middle fingers, respectively. The arrow remained on the screen until participants responded (max = 2.5 sec). The next trial started after a 1.5 sec interval, during which the black screen remained blank. On stop trials, which accounted for 25% of the trials, the arrow stimulus was replaced with a Stop signal (a red vertical bar) after a variable delay (Stop signal delay). We instructed participants to inhibit their response when the Stop signal appeared, and if they did so, the red bar remained on the screen for 2.5 sec. If participants erroneously pressed one of the arrow keys, the red bar disappeared immediately. The next trial started after a 1.5 sec interval.

The Stop signal delay interval started at 250 msec and was adjusted using an adaptive staircase method (Band, van der Molen, & Logan, 2003). If participants successfully inhibited their response on a Stop trial, the Stop signal delay interval was decreased by 50 msec the next time a Stop signal appeared, thereby making it harder to exert inhibitory control. If participants failed to inhibit themselves on a Stop trial, the Stop signal delay interval was increased by 50 msec for the next Stop trial. The algorithm ensured that each participant could inhibit roughly 50% of all Stop trials by the end of the experiment. This design allowed each participant to perform at his or her own inhibition threshold, equated the level of difficulty experienced by participants, and controlled for individual differences in speed of responding (Gauget, et al., 2004).

We explained to the participants that they would not always be able to withhold their response on Stop trials because the computer would adjust the difficulty of the task according to their performance level. We also asked them not to delay their response in anticipation of the Stop signal, but to inhibit their response only when they saw the Stop signal. Participants completed 180 go and 60 Stop trials in 5 blocks, with each block containing 36 Go and 12 Stop trials (240 trials total with an equal number of left- and right-pointing arrows in each block). Data analysis was limited to the fifth block to allow the staircase algorithm to converge on each participant's inhibitory threshold. Limiting the analysis to the fifth block ensured that all participants were performing at the same threshold—defined as the amount of advance warning an individual required to inhibit a habitual response 50% of the time.

Genotyping

We extracted DNA from the venous blood of all participants using a QIAcube robotic workstation (Qiagen, Hilden, Germany). Aliquots of DNA were sent to Partners HealthCare Center for Personalized Genetic Medicine for genotyping. The *DRD2* C957T (rs6277), *DRD3* Ser9Gly (rs6280), and *COMT* Val158Met (rs4680) polymorphisms were genotyped using Sequenom hME chemistry, and the *DRD4* exon III VNTR was genotyped using a

previously published protocol (Eisenberg et al., 2007). In our sample, 23, 69, and 31 patients carried the *COMT* Val/Val, Val/Met, and Met/Met genotypes, respectively. The *DRD2* C957T breakdown was 21 C/C, 62 C/T, and 42 T/T. These distributions did not depart from the Hardy-Weinberg equilibrium (*COMT*: $\chi^2 = 1.975$, $df = 1$, $p = 0.160$; *DRD2*: $\chi^2 = 0.132$, $df = 1$, $p = 0.716$), indicating that allele frequencies were in equilibrium in our cohort. Because only 8 and 12 participants fell in the *D4.7+* and *DRD3* C/C groups, respectively, we excluded *DRD3* and *DRD4* from further analyses.

Statistical analyses

All data were analyzed using MATLAB 2009a (MathWorks Inc., Natick, MA) and SPSS 11.5 (SPSS Inc., Chicago, IL). The principal dependent variable was the SSRT, measured by subtracting the average Stop signal delay from the average correct Go reaction time in the final block of trials (Band, et al., 2003). We also examined the participants' reaction times and error rates on Go trials. A univariate analysis of covariance (ANCOVA) compared each variable of interest among different genetic subgroups. The ANCOVA included *COMT* enzyme activity (Chen, et al., 2004) as a covariate, as well as age and sex because previous research had uncovered age and sex differences in cognitive control ability (Carver, Livesey, & Charles, 2001; Li et al., 2009). We also included LEDD, disease duration, and UPDRS motor scores as covariates in the model to control for differences among participants in dopamine replacement dosage and the severity of motor symptoms.

To examine the impact of training on inhibitory ability, we compared SSRTs in the first and fifth blocks of the experiment. Because the staircase algorithm may not have converged to the 50% inhibitory threshold in the first block for all participants, we first corrected SSRTs for inhibition thresholds—defined as the number of successfully inhibited trials—in each block, and then calculated a repeated measures ANCOVA on the adjusted SSRTs. We followed significant ANCOVA results with follow-up pairwise tests.

Results

We characterized the participants in terms of age, sex, PD duration, H&Y stage, LEDD, number on agonists, MMSE, BDI, and education across *COMT* genotypes (Table 2). A significantly greater number of *DRD2* C/C individuals were taking dopamine agonists as compared to C/T and T/T carriers ($\chi^2 = 6.915$, $df = 2$, $p = 0.032$). Individuals with the C/T genotype of *DRD2* were slightly, but significantly, older than C/C and T/T patients (C/C: $M = 63.4$, $SD = 8.7$; C/T: $M = 68.6$, $SD = 8.4$; T/T: $M = 64.4$, $SD = 8.5$; C/T vs. C/C: $p = 0.048$; C/T vs. T/T: $p = 0.048$). This age difference was taken into account by including age as a covariate in all analyses. Patients were well matched on all other characteristics across *DRD2* genotypes (Table 3).

Because the green arrow in the Go trials was visible for only 2.5 sec, we examined whether any participants missed this response window. Among the 123 participants, 117 (95.1%) never missed the window, while 6 (4.9%; 2 *COMT* Val/Met & *DRD2* C/C, 3 *COMT* Val/Met & *DRD2* T/T, 1 *COMT* Met/Met & *DRD2* T/T) participants missed the window on a single Go trial. The number of successfully inhibited trials did not differ statistically among *DRD2* and *COMT* genotypes.

We used a univariate ANCOVA with SSRT as the dependent variable and genotype as the independent factor to examine the effect of *COMT* variation on SSRT (Figure 2A), with age, sex, disease duration, total LEDD, and UPDRS motor scores as covariates. The main effect of *COMT* on SSRT was significant ($F_{2,115} = 3.56$, $p = 0.032$, $\eta^2 = 5.8\%$). Planned follow-up comparisons revealed that Val/Met and Met/Met participants had significantly higher SSRT thresholds than Val/Val individuals (Val/Met vs. Val/Val: $p = 0.005$ one-sided; Met/Met vs. Val/Val: $p = 0.02$ one-sided). *COMT* did not significantly affect Go trial accuracy ($F_{2,115} = 0.44$, $p = 0.65$) or reaction times ($F_{2,115} = 1.77$, $p = 0.18$) (Figure 2B and C). The effect of *DRD2* on SSRT ($F_{2,115} = 0.34$, $p = 0.72$), Go trial accuracy ($F_{2,115} = 2.7$, $p = 0.07$), and Go trial reaction times ($F_{2,115} = 0.44$, $p = 0.65$) was not significant.

To examine whether *COMT* variation interacted with training, we compared SSRTs in the first and fifth blocks. Because SSRT thresholds were significantly different between the two blocks ($p = 4.04 \times 10^{-12}$), we first corrected the SSRTs in both blocks for this threshold difference: For each block, we carried out a regression analysis with the SSRT as the dependent variable and the percentage of successfully inhibited trials as the independent variable. We then compared the standardized residuals from the two regressions, using a repeated measures ANCOVA with the standardized residuals as the dependent variables, and *COMT* genotype as the between-subjects factor. In both blocks, Val/Val carriers had lower standardized residuals (indicating better inhibitory ability) than those with at least one Met allele. Neither the main effect of the experimental block ($F_{1,115} = 1.09$, $p = 0.30$) nor the interaction between block and genotype ($F_{2,115} = 0.85$, $p = 0.43$) was significant.

Discussion

This study examined whether polymorphisms in *COMT*, *DRD2*, *DRD3*, and *DRD4* modulate inhibitory ability in PD. We predicted that those individuals with variants that increase dopamine signaling would have reduced inhibitory ability due to a dopamine overdose in networks that are relatively preserved in the early stages of the disease. As predicted, patients who carried at least one Met allele of *COMT*, which confers increased dopamine levels in the PFC, had longer SSRTs than non-carriers. This reduction in inhibitory control was not accompanied by changes in accuracy or reaction times in trials without a Stop signal, indicating that increased SSRT was not due to changes in performance or to a general slowing of reaction times. Unlike *COMT*, *DRD2* variation did not alter the SSRT. Small sample sizes prevented us from examining the influence of *DRD3* and *DRD4* on the SSRT.

The major finding of this experiment was that the Met allele of *COMT* resulted in a selective decrease in inhibitory ability in PD patients taking dopamine replacement therapy. Critically, this cognitive deficit was consistent with our prediction based on previous results showing an inverted-U relation between dopamine signaling and inhibitory ability. This finding highlights the future possibility of optimizing an individual's dopamine replacement therapy regimen based on his or her unique genetic profile.

Impact of COMT Val158Met polymorphism on SSRT

The observed effect of the *COMT* Val158Met polymorphism is consistent with the known neural substrates of response inhibition. Investigators have shown that normal function of the PFC, particularly the right inferior frontal gyrus, is essential for successful response inhibition (Aron, 2010). Further, too much dopamine in the PFC results in a general reduction in neuronal activity (Arnsten, 2011; Kroener, Chandler, Phillips, & Seamans, 2009; Wang, Vijayraghavan, & Goldman-Rakic, 2004). In mice, investigators showed that the application of high concentrations of dopamine to the PFC significantly reduced the number of action potentials produced by pyramidal neurons (Kroener, et al., 2009). Similarly, in well-trained monkeys performing spatial working memory tasks, high levels of D1 agonists significantly reduced the delay period activity of pyramidal neurons (Arnsten, 2011; Wang, et al., 2004). Thus, it is likely that our PD patients with at least one Met allele of *COMT* had slowed SSRTs because of a reduction of neural activity in the PFC due to a dopamine overdose, but we cannot rule out the possibility that the impact of *COMT* stemmed from its action at other nodes of the inhibitory network (e.g., pre-supplementary motor area or subthalamic nucleus). Future functional imaging studies on the impact of the *COMT* Val158Met variation on response inhibition in PD patients may be able to localize specific nodes of interaction between dopamine replacement therapy and *COMT* variation.

No link between DRD2 C957T polymorphism and SSRT

The lack of a *DRD2* effect on response inhibition was surprising. D₂ receptors are densely expressed in the basal ganglia (including the caudate and putamen), which constitute nodes of the response inhibition network. A previous study reported that healthy adults with variants of *DRD2* that increased the expression of D₂ receptors had better inhibitory control than those with reduced D₂ expression levels (Hamidovic, Dlugos, Skol, Palmer, & de Wit, 2009). Similarly, alcoholic carriers of the A1 allele of the *ANKK1* Taq1A polymorphism, which is in linkage disequilibrium with *DRD2* C957T and is associated with a 30% to 40% reduction in D₂ receptor density in the striatum, had poorer inhibitory control than A2/A2 carriers (Rodriguez-Jimenez et al., 2006). Further, PD patients who performed at the same level as controls in the Go/NoGo task had increased activity in the right caudate relative to controls, highlighting the importance of the striatum for response inhibition (Baglio et al., 2011).

No interaction between COMT and DRD2

Several investigators have shown a significant interaction between *COMT* and *DRD2* polymorphisms in healthy adults. On a verbal working memory task, those with *COMT* Val/Val and *DRD2* C/C genotypes performed worse than those with Met/Met and T/T genotypes (Xu et al., 2007). Further, Met carriers had significantly better working memory manipulation performance relative to Val/Val carriers, but only when they did not carry the A1 allele of the *ANKK1* Taq1A (Stelzel, Basten, Montag, Reuter, & Fiebach, 2009). Thus, to test for a possible interaction, we ran an ANCOVA with SSRT as the dependent variable, *COMT* and *DRD2* as independent variables, and age, sex, disease duration, disease severity, and LEDD as covariates. The main effect of *COMT* remained significant in this model ($p = 0.043$), but as before, the main effect of *DRD2* was not significant. We did not find an

interaction between *COMT* and *DRD2*. Although this finding could be due to our small sample size (only 3 people were Val/Val and C/C carriers), the results suggest that the *COMT* Cal158Met, and not *DRD2* C957T, variation is the critical determinant of inhibitory ability in PD patients who take dopamine replacement therapy.

Training did not alter inhibitory ability among *COMT* genotypes

An open question was whether PD patients could be trained to shorten their time to inhibit their response. To examine this issue, we compared the SSRTs in the first and fifth blocks of our experiment. If training were effective, then SSRTs in the fifth block would be shorter than SSRTs in the first. *COMT* Val/Val carriers had lower SSRTs (adjusted for the difference in stopping threshold between the two blocks) than those with at least one Met allele in both blocks. The main effect of the experimental block and the interaction between block and genotype were not significant, indicating that training did not differentially affect inhibitory ability among *COMT* genotypes.

The lack of a training effect is interesting in light of experimental and computational modeling work, suggesting that PD patients taking dopamine replacement therapy show a selective deficit in learning from negative feedback, whereas patients undergoing deep brain stimulation do not, but instead, tend to respond more impulsively under a variety of task conditions (Frank, Samanta, Moustafa, & Sherman, 2007; Frank, Seeberger, & O'Reilly R, 2004). Interestingly, this computational model found that the best way to simulate the effects of dopaminergic medication were via tonic stimulation of D₂ receptors (Frank, et al., 2007), which effectively eliminates NoGo learning associated with dopamine dips following non-rewarding outcomes (Schultz, 1998). While the design of our task is not conducive to teasing apart whether patients were able to learn from positive or negative feedback, it is important to point out that some of the effects observed here may be due to a medication-induced insensitivity to negative outcomes, rather than pure motor impulsivity per se. It is notable, however, that we did not find a link between *DRD2* polymorphisms and task performance, and dopaminergic activity at D₂ receptors is most closely linked to NoGo learning (Frank, et al., 2007). Further research combining genetic assays with tasks specifically designed to target positive versus negative learning will be needed to fully address this issue.

DRD3 and DRD4

We were unable to examine the influence of *DRD3* and *DRD4* variation on inhibitory control due to the small sample sizes. Because studies in healthy adults have shown a significant impact of *DRD4* variation on inhibitory ability, this polymorphism may play an important role in PD inhibitory ability as well (Congdon, et al., 2008). D₃ receptors are densely expressed in the ventral striatum, which is spared from dopamine loss in the early stages of PD (Gurevich & Joyce, 1999; Murray, Ryoo, Gurevich, & Joyce, 1994). Because most dopamine agonists have a high affinity for D₃ receptors (Mierau et al., 1995), variations in *DRD3* may play a crucial role in determining individual risk for dopamine-induced side effects. A promising topic for future studies would be to examine the effect of *DRD3* and *DRD4* on cognition in large samples of PD patients

Conclusions

The dopamine overdose hypothesis posits that dopamine replacement therapy overloads networks that are relatively spared from dopamine cell death in PD, thus adversely affecting the functions supported by them (Cools, 2006). Here, we advanced this hypothesis by showing that medication-induced changes in behaviors mediated by these circuits also depend on variation in genes of the dopamine system. Specifically, we showed that participants with at least one Met allele of COMT, which is associated with increased dopamine levels in the PFC, exhibited inhibitory ability that was significantly inferior to that of Val/Val carriers. These findings highlight the clinically important idea that PD patients who are Met carriers have an increased risk for developing impulse control behaviors when taking dopamine replacement therapy.

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Figure 1. Sequence of events in the Stop Signal Task

Participants were instructed to respond in the Go trials and to inhibit their responses in the Stop trials. Example sequence of events in the Stop Signal Task: hit left arrow key; hit right arrow key; suppress action to hit right arrow key after seeing the Stop signal (red vertical bar).

Figure 2. SSRT as a function of COMT genotypes

A) Patients with at least one Met allele had a significantly longer SSRT compared to Val/Val carriers. B) The groups did not differ in accuracy. C) The groups did not differ in reaction times on Go trials. Error bars depict *SEM*. * $p = 0.005$ one-sided; # $p = 0.02$ one-sided.

Table 1

Characteristics of PD patients who completed the Stop Signal Task

Variable	PD patients
No. of participants	123 (80M; 43F)
Age (yrs)	66.3 (8.7)
PD duration (yrs)	5.5 (3.8)
	Stage 1 17
H&Y	Stage 2 98
	Stage 3 8
LEDD (mg/day)	610.9 (444.3)
% taking agonists	55.3%
MMSE	28.2 (1.3)
BDI	6.1 (4.1)
Education (yrs)	16.7 (2.9)

Results are presented as the mean (*SD*), number, or percentage.

Table 2

Characteristics of *COMT* subgroups in the Stop Signal Task

Variable	<i>COMT</i>		<i>p</i>
	Val/Val	Val/Met	Met/Met
No. of participants	23	69	31
Age (yrs)	68.0 (6.7)	65.8 (8.7)	66.3 (10.2)
			0.600 §
Sex M:F	13:10	44:25	23:8
			0.382 ¶
PD duration (yrs)	5.0 (3.8)	5.1 (3.8)	6.7 (3.8)
			0.116 §
Stage 1	2	9	6
H&Y	Stage 2	19	55
			24
	Stage 3	2	5
			1
LEDD (mg/day)	557.9 (378.4)	595.4 (434.7)	685.0 (510.8)
			0.533 §
% taking agonists	52.2%	56.5%	54.8%
			0.935 ¶
MMSE	28.0 (1.5)	28.2 (1.3)	28.3 (1.3)
			0.577 §
BDI	5.8 (3.7)	6.0 (4.0)	6.7 (4.5)
			0.688 §
Education (yrs)	16.7 (3.4)	16.7 (3.0)	16.5 (2.4)
			0.951 §

§ ANOVA;

¶ Chi square test;

£ Fisher's exact test.

Results are presented as the mean (*SD*), number, or percentage.

Table 3

Characteristics of *DRD2* subgroups in the Stop Signal Task

Variable	<i>DRD2</i>			<i>p</i>
	C/C	C/T	T/T	
No. of participants	21	62	40	
Age (yrs)	63.4 (8.7)	68.6 (8.4)	64.4 (8.5)	0.013 §
Sex M:F	14:7	42:20	24:16	0.715 ¶
PD duration (yrs)	5.5 (3.3)	5.6 (4.0)	5.3 (3.9)	0.909 §
Stage 1	6	7	4	
H&Y	15	50	33	0.267 £
Stage 3	0	5	3	
LEDD (mg/day)	616.4 (325.1)	582.6 (455.8)	651.9 (485.1)	0.746 §
% taking agonists	81.0%	48.4%	52.5%	0.032 ¶
MMSE	28.5 (1.2)	28.3 (1.3)	27.8 (1.3)	0.070 §
BDI	6.1 (3.4)	5.7 (4.1)	6.8 (4.4)	0.404 §
Education (yrs)	17.2 (2.3)	16.9 (3.1)	16.2 (2.9)	0.324 §

§ ANOVA;

¶ Chi square test;

£ Fisher's exact test.

Results are presented as the mean (*SD*), number, or percentage.

Significant results are in bold font.