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van Wouwe, N.C.; Kanoff, K.E.; Claassen, D.O.; Spears, C.A.; Neimat, J.S.; van den Wildenberg, W.P.M.; Wylie, S.A.

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Dissociable Effects of Dopamine on the Initial Capture and the Reactive Inhibition of Impulsive Actions in Parkinson's Disease

Nelleke C. van Wouwe[1], Kristen E. Kanoff[1], Daniel O. Claassen[1], Charis A. Spears[1], Joseph Neimat[1], Wery P. M. van den Wildenberg[2], and Scott A. Wylie[1]

Abstract

■ Dopamine plays a key role in a range of action control processes. Here, we investigate how dopamine depletion caused by Parkinson disease (PD) and how dopamine restoring medication modulate the expression and suppression of unintended action impulses. Fifty-five PD patients and 56 healthy controls (HCs) performed an action control task (Simon task). PD patients completed the task twice, once withdrawn from dopamine medications and once while taking their medications. PD patients experienced similar susceptibility to making fast errors in conflict trials as HCs, but PD patients were less proficient compared with HCs at suppressing incorrect responses. Administration of dopaminergic medications had no effect on impulsive error rates but significantly improved the proficiency of inhibitory control in PD patients. We found no evidence that dopamine precursors and agonists affected action control in PD differently. Additionally, there was no clear evidence that individual differences in baseline action control (off dopamine medications) differentially responded to dopamine medications (i.e., no evidence for an inverted U-shaped performance curve). Together, these results indicate that dopamine depletion and restoration therapies directly modulate the reactive inhibitory control processes engaged to suppress interference from the spontaneously activated response impulses but exert no effect on an individual's susceptibility to act on impulses. ■

INTRODUCTION

Parkinson disease (PD) progressively and invariably compromises the brain's dopamine system and, concomitantly, an individual's speed and precision at initiating, switching, and inhibiting actions. Establishing links between dopamine and specific aspects of action control is not only critical to developing better models and interventions for human PD but also to advancing our understanding of how dopamine modulates key cognitive control circuitries in the brain.

Clues about dopamine's involvement in action control arise from consistent demonstrations that individuals with PD have difficulty reacting quickly in times of conflict. In many action-oriented situations, the brain is inundated by visual information that may or may not be relevant for directing desired action choices. Irrelevant visual information can sometimes trigger spontaneous action impulses that conflict with goal-relevant actions. If the activated impulse is of sufficient strength, an individual may react impulsively in error. But even in the absence of an overt action error, the activation of conflicting response impulses can interfere with the speed of executing goal-relevant actions. The magnitude of this slowing is called the "interference effect," which is produced with exceptional robustness in response conflict paradigms, such as the Simon task and the Flanker task, that contrast performance on trials in which an action impulse corresponds versus conflicts with a desired action choice (Wylie et al., 2009a, 2009b; Wylie, Ridderinkhof, Bashore, & van den Wildenberg, 2010; Eriksen & Eriksen, 1974; Simon, 1969).

In PD, mean interference effects are commonly, yet not always, exacerbated compared with healthy controls (HCs). The mixed findings may in part reflect individual differences in the effects of dopamine on performance as most studies have tested PD patients while taking their dopamine medications. Another source of the inconsistency comes from the fact that mean interference effects mask two dynamic processes that underlie conflict and its resolution: (1) the strength of the initial activation of response impulses (coined "impulse capture") and (2) the reactive inhibitory control engaged to suppress these impulses. The Dual Process Activation-Suppression (DPAS) postulates that, in conflict situations, conflicting stimulus information directly activates an incorrect action impulse (direct processing route) that conflicts with the deliberate processing of the goal-relevant stimulus and selection of the appropriate response (deliberate processing route; Ridderinkhof, 2002; see also van den Wildenberg et al., 2010). The model further asserts that, upon detecting the activation of an incorrect response, an inhibition mechanism is engaged to selectively suppress this incorrect response activation, ultimately

[1]Vanderbilt University Medical Center, [2]University of Amsterdam

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counteracting and reducing interference with the deliberate processing route. These dynamic processes (impulse capture, reactive inhibition) can be dissociated by analyzing interference effects across the full range of the RT distribution. Strong impulse capture is inferred by higher rates of fast impulsive errors and increased interference effects across faster segments of the RT distribution. This pattern completely reverses toward slower segments of the RT distribution as inhibition processes come online to suppress interfering response impulses. The DPAS model prescribes a set of distributional analytic tools (conditional accuracy functions [CAFs] and delta plots) that can isolate and quantify the relative strength of impulse capture and the proficiency of inhibitory control (Ridderinkhof, 2002; see also van den Wildenberg et al., 2010).

Initial studies of dopamine-medicated PD patients using the DPAS model suggest that PD does not alter the strength of impulse capture but selectively compromises the proficiency of inhibiting conflicting response impulses. That this effect may be dopamine dependent is suggested by two recent studies. We recently reported that selective withdrawal from dopamine agonist medication modulated inhibitory control, but not impulse capture, in PD patients, but that the direction of dopamine agonist effects on inhibitory control for a given patient depended on his or her baseline performance in the dopamine agonist withdrawn state (Wylie et al., 2012). Notably, patients did not withdraw from their levodopa medications in that study; thus, these studies were limited to the selective effect of dopamine agonist medication on action control.

The DPAS framework was also applied in a recent study of Simon task performance in 12 young healthy adults taking an amino acid mixture that selectively depletes dopamine precursor activity (Ramdani et al., 2015). Compared with a placebo condition, young adults in a state of depleted dopamine synthesis showed no changes in impulse capture (i.e., fast impulsive errors) but showed a selective reduction in the proficiency of inhibiting response impulses. It remains unclear from this study though to what extend dopamine in the brain was interrupted by reducing dopamine precursor activity in healthy participants, whereas in PD, we can be confident of at least 50% or greater dopamine cell loss with symptom onset (Kordower et al., 2013; Bernheim, Birkmaye, Hornykie, Jellinge, & Seitelbe, 1973).

Together, these initial findings point to the putative role for dopamine modulation in inhibitory control processes that are critical to resolving response conflict as well as to individual differences in the effects of dopamine on action control. However, it is unknown how different types of dopamine (DA) medication modulate inhibitory control. This is important as different medications are often presumed to have somewhat distinct effects on the balance of direct and indirect BG pathways (i.e., the precursor levodopa presumably affects both pathways whereas DA agonists like would selectively modulate the D2 receptors of the indirect pathway).

The primary goal of the current study of PD was to directly test if and how different dopaminergic drugs (i.e., dependent on the type of medication) modulate inhibitory control processes during conflict. Using the Simon task and the DPAS framework, we tested the effects of dopaminergic medications on impulse capture and the proficiency of inhibitory control in a large sample of PD patients (n = 55) tested during withdrawn and active dopaminergic medication states. First, we investigated if the effects of dopaminergic medications on inhibitory control may depend on the type of dopamine medication. Medicated PD patients generally take two main classes of dopaminergic drugs, precursors (i.e., levodopa) and agonists. Precursors lead to greater production of dopamine from intact neurons, thus impacting both D1 and D2 dopamine receptor families. In contrast, dopamine agonists (e.g., ropinirole, pramipexole) mimic dopamine and exert selective effects on D2 family dopamine receptors. Because dopamine acting at D1 receptors is thought to stimulate the BG direct pathway (i.e., the action "go" pathway) and at D2 receptors to suppress the indirect pathway (i.e., the action "no-go" pathway), the type of dopaminergic drug may be critical to the direction and magnitude of effects on inhibitory action control. This is relevant from both a clinical perspective (how do different types of medication affect inhibitory control in PD) as well as to increase our understanding of the neurocognitive mechanism (how does DA modulation of the different DA pathways affect inhibitory control).

Second, the effects of dopaminergic medication on inhibitory control may be less related to the specific type of dopaminergic drug, but instead to how dopaminergic medications achieve an optimal level of dopamine in the brain and restore balance between the BG direct and indirect pathways. In fact, recent evidence suggests that as many as 60% of medium spiny neostriatal neurons send efferent projections along both direct and indirect BG pathways and that both pathways express D1 and D2 receptors (Calabresi, Picconi, Tozzi, Ghiglieri, & Di Filippo, 2014; Huerta-Ocampo, Mena-Segovia, & Bolam, 2014). If there is indeed overlap of receptor types across direct and indirect pathways, both levodopa (impacting D1 and D2 receptors on both pathways) as well as DA agonists (thought to selectively affect D2 in the indirect pathway) could yield comparable results because they would both modulate direct and indirect pathways. Thus, dopamine precursors and agonists may be better conceptualized with respect to the general impact on the coordinated activities of these pathways (Calabresi et al., 2014). Consistent with this notion, accruing evidence suggests that the relationship between dopamine levels and performance of several cognitive control processes is best characterized by an inverted U-shaped curve (Vijayraghavan, Wang, Birnbaun, Williams, & Arnsten, 2007; Gibbs & D'Esposito, 2005; Cai & Arnsten, 1997). Thus, optimal performance depends on an optimal level of dopamine, with diminished or excessive levels of dopamine compromising cognitive

performance. A direct implication is that baseline cognitive performance in PD patients withdrawn from dopaminergic medications may be critical to determining cognitive effects of dopaminergic medications (Cools & D'Esposito, 2011; Williams-Gray, Hampshire, Robbins, Owen, & Barker, 2007). Specifically, patients showing clear signs of inhibitory control deficits at baseline (due presumably to diminished dopamine levels in these circuits) would be predicted to show improved inhibition as dopaminergic medications shift dopamine levels and performance toward a more optimal range. In contrast, patients showing normal or near-normal inhibitory control at baseline (and presumably relatively more preserved dopamine levels in these circuits, which might still be diminished compared with a healthy brain) might show no change or might even be compromised as dopaminergic medications shift performance on the inverted U-shaped curve. Thus, the impact of dopamine medications on action control in times of conflict may depend less on the specific type of dopaminergic drug, but instead on how the state of the action control system and the coordinated activities between direct and indirect pathways at baseline (i.e., when dopaminergic drugs are withdrawn) are altered by increasing dopamine function.

METHODS

Participants

PD participants (n = 55) were recruited from the Movement Disorders Clinic at Vanderbilt University Medical Center, and HCs (n = 56) were recruited from community advertisement or as qualifying family members of PD participants. The 56 HC participants included 26 HC participants newly recruited for this study and an additional 30 HC participants who had participated in a prior study with the same experimental task (Wylie et al., 2010). All participants met the following exclusion criteria: no history of (i) neurological condition (besides PD); (ii) bipolar affective disorder, schizophrenia, or other psychiatric condition known to compromise executive cognitive functions; or (iii) severe mood disorder or medical condition known to interfere with cognition (e.g., diabetes, pulmonary disease). A movement disorder neurologist diagnosed PD, and all patients were treated currently with levodopa monotherapy (n = 25), dopamine agonist monotherapy (n = 10), or levodopa plus agonist dual therapy (n = 20). PD motor symptoms were graded using the Unified Parkinson Disease Rating Scale (UPDRS) motor subscore; additionally, they all received a rating of Stage III or less using the Hoehn and Yahr Scale (Hoehn & Yahr, 1967). On the basis of these data, each PD participant was experiencing mild to early moderate symptoms. Dosages for the dopamine medications were converted to levodopa equivalent daily dose (LEDD) values (Weintraub et al., 2006).

All PD patients performed at a level on the Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2005) that ruled out dementia but permitted very mild to minimal gross cognitive difficulties (all scores ≥ 23). HCs all scored greater than a 26 (mean = 28, SD = 1.3) on the MOCA or greater than 27 (mean = 29, SD = 1.0) on the Mini Mental Status Examination (Folstein, Folstein, & McHugh, 1975). All participants reported stable mood functioning and the absence of major depression during a clinical interview, but we allowed endorsements of mild to low moderate symptoms of depression on the Center for Epidemiological Studies Depression (CESD) questionnaire. The mean CESD scores for both groups (HC = 8, PD = 14) were below the standard cutoff score of 16 that is suggestive of the presence of mild depressive symptoms. As described in the Results section, neither depression nor mental status scores were related to the primary experimental task performance measures in the PD group. All participants had corrected-to-normal vision. They all provided informed consent before participating in the study in full compliance with the standards of ethical conduct in human investigation as regulated by Vanderbilt University.

Experimental Task and Procedures

The Simon task was administered on a PC computer with a monitor placed approximately 1 m in front of the participant. Handheld response grips registered responses via a left or right thumb press made on a button at the end of each grip. The beginning of a block of trials was signaled by the appearance of a small, centrally located black-colored square (i.e., a fixation point) against a light gray-colored screen. The fixation point remained on the screen for an entire duration of a block of trials. Within a variable duration of 1750–2250 msec following the initial appearance of the fixation point, a blue or green circle (diameter 2.1 cm; visual angle 1.20°) appeared 0.6 cm (0.34° visual angle) to the left or to the right of fixation and remained on the screen until the participant either made a response or a 1500-msec time limit elapsed. Next, a variable intertrial interval of 1750–2250 msec elapsed before the next trial was initiated by the appearance of another blue or green circle. The end of a block of trials was indicated by the offset of the fixation mark and printed instructions to take a brief break before the start of the next block of trials.

Participants were instructed to respond on the basis of a predetermined mapping between the color of the circle and a response hand (e.g., green circle = right thumb press; blue circle = left thumb press). The mappings between color and response hand were counterbalanced across participants but preserved across testing sessions within individuals. Participants were encouraged to maintain the focus of their visual attention on the fixation point and to respond as quickly and as accurately as possible. To elicit the Simon effect, two trial types manipulated the correspondence between the spatial location of the circle and the response signaled by its color. For Corresponding (Cs) trials, the circle appeared to the side of fixation that

matched the response side signaled by the color of the stimulus (e.g., a green circle calling for a right-hand response appeared to the right side of fixation). For Noncorresponding (Nc) trials, the circle appeared on the side of fixation opposite the side of the response signaled by the circle's color (e.g., a green circle calling for a right-hand response appeared on the left side of fixation). Cs and Nc trial types were presented randomly, but with equal probability, within each block of trials. In total, participants completed 60 practice trials followed by 240 experimental trials (i.e., 4 blocks of 60 trials) equally divided among Cs and Nc trial types.

HC participants completed just one session of the Simon task. PD participants completed two sessions, once while taking all of their prescribed dopaminergic medications and in their optimal "on" phase of their medication cycle and a second time following a 36- to 48-hr withdrawal from their dopaminergic medication (levodopa: 36 hr; agonist: 48 hr). The order of visits was counterbalanced across PD participants and completed at approximately the same time of day. Importantly, no changes in medication dosages or addition or discontinuation of either drug for clinical purposes were made at any time during study participation.

Statistical Techniques

RT latencies for Cs and Nc trials faster than 180 msec (i.e., anticipatory reactions) and slower than 3 standard deviations of the mean within each condition and judged as clear outliers following visual inspection were excluded but accounted for fewer than 1% of trials across participants (Wylie et al., 2010). Mean RT and square root transformed accuracy rates were computed for each level of Correspondence to analyze mean interference costs on response latency and accuracy.

The DPAS model specifies a distributional analytical framework for dissociating two temporally distinct cognitive processes that are engaged in conflict tasks and masked in traditional mean interference costs. The first process, impulse capture, is reflected by the proportion of fast, impulsive errors that are easily visualized and measured in plots of accuracy rates against RT (i.e., a CAF) for each level of Correspondence (van den Wildenberg et al., 2010; Wylie et al., 2010; Kornblum, Hasbroucq, & Osman, 1990). Accuracy rates from the fastest RT bin of the CAFs for Nc trials are the most sensitive measures of the strength of initial impulse capture (see van den Wildenberg et al., 2010).

The second process reflects top–down inhibitory control that is engaged more slowly and builds up to suppress the interference produced by the conflicting action impulse (Ridderinkhof, 2002). Proficient inhibitory control is assumed to be most evident at the slow end of the RT distribution, because it takes time for this control to build up after it has been triggered by the conflicting response impulse. Plotting the magnitude of the Simon interference effect (RT Nc trials minus RT Cs trials) as a function of response speed (i.e., a delta plot) yields a pattern of increasing interference across fast to intermediate response latencies that is followed by a dramatic and statistically deviant reduction (cf., Luce, 1986) in interference toward the slow end of the distribution (Proctor, Miles, & Baroni, 2011). The DPAS model asserts that the slope of the interference reduction at the slowest segment of the delta plot provides the most sensitive metric of the proficiency of inhibitory control over conflicting motor impulses, an assertion supported empirically across several studies using both nonclinical and clinical populations (Wylie et al., 2009a, 2009b, 2010; Wijnen & Ridderinkhof, 2007; Wylie, Ridderinkhof, Eckerle, & Manning, 2007; Bub, Masson, & Lalonde, 2006; Ridderinkhof, Scheres, Oosterlaan, & Sergeant, 2005; Burle, Possamai, Vidal, Bonnet, & Hasbroucq, 2002; for a review, see Ridderinkhof, Forstmann, Wylie, Burle, & van den Wildenberg, 2011).

Because HC participants completed testing just once, our first set of analyses compared PD participants in their dopamine withdrawn state (i.e., "off" state) and HC participants on mean interference effects (RT, accuracy), impulse capture (CAF), and proficiency of inhibitory control (delta plot) using separate repeated-measures ANOVAs and t tests as appropriate. The second set of analyses focused on PD participants and tested the effects of Dopamine State (off, on) and PD Subgroup (levodopa monotherapy, agonist monotherapy, levodopa/agonist dual therapy) on these measures. A third analysis addressed the association between baseline inhibitory control proficiency in the medication-withdrawn state and the change in inhibitory control because of dopamine medication, including a test of the equality of the variances in the two conditions to account for regression to the mean and the inherent correlation between initial and change value (Tu & Gilthorpe, 2007; Geenen & van de Vijver, 1993; Myrtek & Foerster, 1986; see also Wylie et al., 2012, for similar application in PD). Finally, exploratory Pearson correlations (with p value adjustments for multiple comparisons) were computed to test associations between several clinical features of PD (e.g., dopamine dosage, UPDRS score in off state, MOCA scores, disease duration, age) and interference effects, impulse capture, and inhibitory control measured in the off medication state.

To quantify the strength of our findings more appropriately than with standard significance testing (Wagenmakers, 2007), the main hypotheses were also examined by calculating a Bayes factor using Bayesian Information Criteria (Jarosz & Wiley, 2014; Rouder, Morey, Speckman, & Province, 2012; Wetzels, Grasman, & Wagenmakers, 2012). The Bayes factor (BF_{01}) provides the odds ratio for the null versus the alternative hypotheses given a particular data set. A value of 1 means that null and alternative are equally likely, larger values suggest that the data are in favor of the null hypothesis, and smaller values indicate that the data are in favor the alternative hypothesis. We

used JASP 7.0 (Love et al., 2015) to calculate the Bayes factor.

RESULTS

Analysis of Sample Demographics

Table 1 shows that HC and PD groups were similar in age, education, and sex distribution (all ps > .05). Among the three PD medication subgroups, the only differences included longer disease duration among patients on dual therapy (~6 years) compared with both monotherapy groups (~3 years) and higher total LEDD for patients on levodopa monotherapy and dual therapy compared with patients on agonist monotherapy, which is not entirely unexpected given agonist conversion values. Otherwise, the three patient subgroups were similar in age, education, sex distribution, mental status scores, QUIP scores, and UPDRS scores in the dopamine-withdrawn state (all ps > .10).

Performance of PD Patients "Off" Dopamine Medications versus HCs

Mean Interference Effects on RT and Accuracy (Figure 1)

Overall, PD patients in their withdrawn (i.e., off) medication state were 36 msec slower to respond than HCs, but equally as accurate ([PD vs. HC: RT 520 vs. 482 msec; accuracy 96.2% vs. 96.9%] Group: RT, $F(1, 109) = 5.52$, $p = .02$; accuracy, $F(1, 109) = 0.87$, $p = .35$). A robust Simon effect was produced across participants, which was revealed by reactions that averaged 40 msec slower and 4% less accurate for Nc compared with Cs trials (Correspondence: RT, $F(1, 109) = 378.44$, $p < .001$; accuracy, $F(1, 109) = 37.0$, $p < .001$). The magnitude of the Simon effect on RT was significantly larger among PD patients (46 msec) compared with HCs (34 msec), but the Simon effect costs to accuracy rates were similar between the groups (PD: 3.4%; HC: 2.2%) (Group × Correspondence: RT, $F(1, 109) = 8.67$, $p = .004$; accuracy, $F(1, 109) = 1.35$, $p = .25$).

Response Capture by Incorrect Action Impulses (Figure 2A and B)

Consistent with the DPAS model, CAFs revealed a pattern of higher rates of fast errors on Nc compared with Cs trials at the early bins of the RT distribution, but similar accuracy rates at intermediate and slower RT latency bins (Figure 2A and B). To analyze these patterns, we first included all bins of the CAFs in the analysis (Bins factor) before focusing in on our primary group comparison of accuracy rates at the fastest RT bin (i.e., to measure rates of fast, impulsive action errors). We report the interaction terms containing the Bins factor, as the

Table 1. Sample Characteristics

		PD			
	HC	*All*	*Levo Mono*	*Dual Therapy*	*DAA Mono*
Sample size (n)	56	55	25	20	10
Age (years)	62.2 (7.0)	63.7 (8.1)	65.5 (9.1)	61.5 (6.7)	63.7 (7.8)
Sex (M:F)	29:27	236:19	19:6	13:7	4:6
Education (years)	16.2 (3.2)	15.5 (2.5)	15.8 (2.3)	15.2 (2.6)	15.2 (2.7)
MOCA* (n = 26)	28.1 (1.4)	26.0 (2.4)	25.8 (2.5)	26.5 (2.4)	25.1 (2.4)
MMSE (n = 30)	29.5 (1.0)				
QUIP-ICD	–	10.3 (7.4)	9.3 (6.9)	11.2 (6.9)	11.1 (9.7)
QUIP-Total	–	21.5 (13.5)	20.6 (13.0)	21.8 (11.5)	23.3 (19.0)
LEDD**	–	732.0 (431.2)	707.2 (405.4)	1006.0 (332.1)	246.0 (116.3)
Disease duration (years)***	–	4.4 (3.4)	3.2 (2.4)	6.3 (3.7)	3.3 (3.5)
UPDRS motor	–	26.9 (12.8)	23.8 (10.6)	32.1 (14.1)	23.8 (12.6)

Values provided are means (with standard deviation in parentheses).

AMNART = American modification of the National Adult Reading Test; CES-D = Center for Epidemiological Studies-Depression Scale; DAA = dopamine agonist monotherapy; Levo Mono = levodopa monotherapy; MMSE = Mini Mental Status Examination; QUIP = Questionnaire for Impulsive-Compulsive Disorders (ICD includes only the following behaviors: gambling, sexual behavior, buying, and eating).

*$p < .05$, comparing HC with MOCA (n = 26) to all PD.

**$p < .05$, contrasting DAA Mono to Levo Mono and Dual Therapy.

***$p < .05$, contrasting Dual Therapy to DAA Mono and Levo Mono.

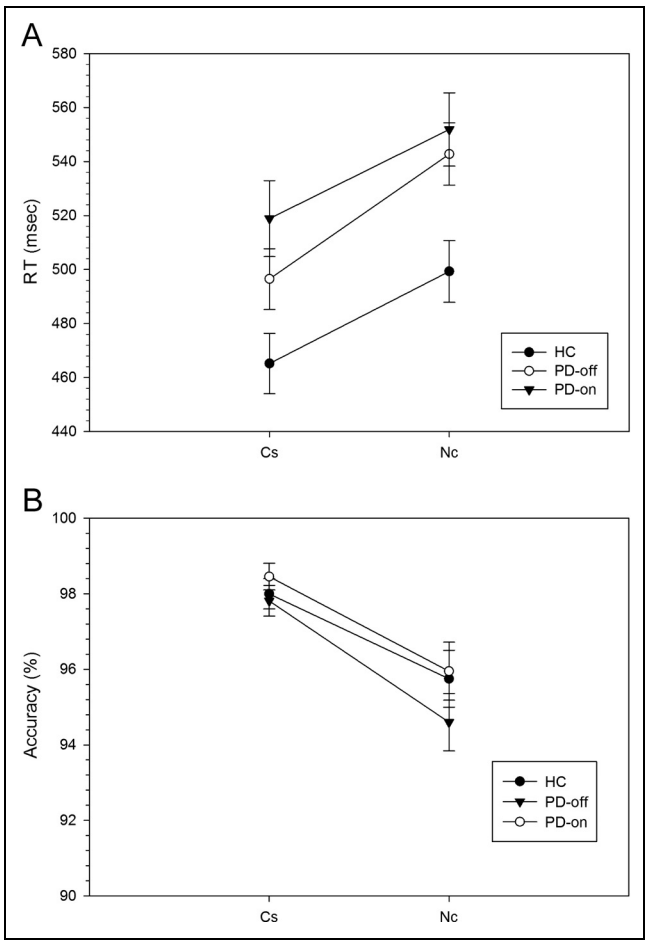

Figure 1. Mean RTs (A) and accuracy rates (B) on corresponding (Cs) and noncorresponding (Nc) trial types for HCs and PD participants in off and on dopamine medication states. Error bars reflect *SEM*s.

relationships between the Group and Correspondence factors remained, not surprisingly, consistent with the mean accuracy analyses reported above. Error rates varied across RT bins (Bins: $F(6, 104) = 11.43$, $p < .001$), and a clear difference was measured in the percentage of errors for Cs and Nc trials across bins of the RT distribution (Bins × Correspondence: $F(6, 104) = 14.36$, $p < .001$). On Nc trials, a pronounced pattern of fast errors was followed by a dramatic reduction in errors at intermediate and slow speeds. In contrast, the entire range of response latencies for Cs trials was associated with low error rates. It is apparent as well that the patterns of errors across bins were not influenced differentially by Group (Group × Bins: $F(6, 104) = 1.35$, $p = .24$; Group × Bins × Correspondence: $F(6, 104) = 1.14$, $p = .34$). Even a focused analysis on the fastest bin of accuracy rates confirmed that the higher percentage of fast impulsive errors on Nc compared with Cs trials (Correspondence, $F(1, 109) = 77.45$, $p < .001$) was similar across Groups (Group × Correspondence, $F(1, 109) = 0.03$, $p = .85$, $BF_{01} = 7.3$).

The estimated Bayes factor (null/alternative) suggested that the data were 7.3:1 in favor of the null hypothesis or 7.3 times more likely to occur under a model without including an interaction effect of Group × Correspondence, rather than a model with it.

Within the conceptual framework of the DPAS model, these results support the conclusion that the strength of capture by incorrect response impulses was similar across PD and HC groups.

Suppressing Interference from Action Impulses (Figure 3)

We first included delta values from all bins of the delta plot in the analysis (Bins factor) before focusing in on our primary comparison of the final delta plot slope (i.e., to measure proficiency of inhibitory control). We

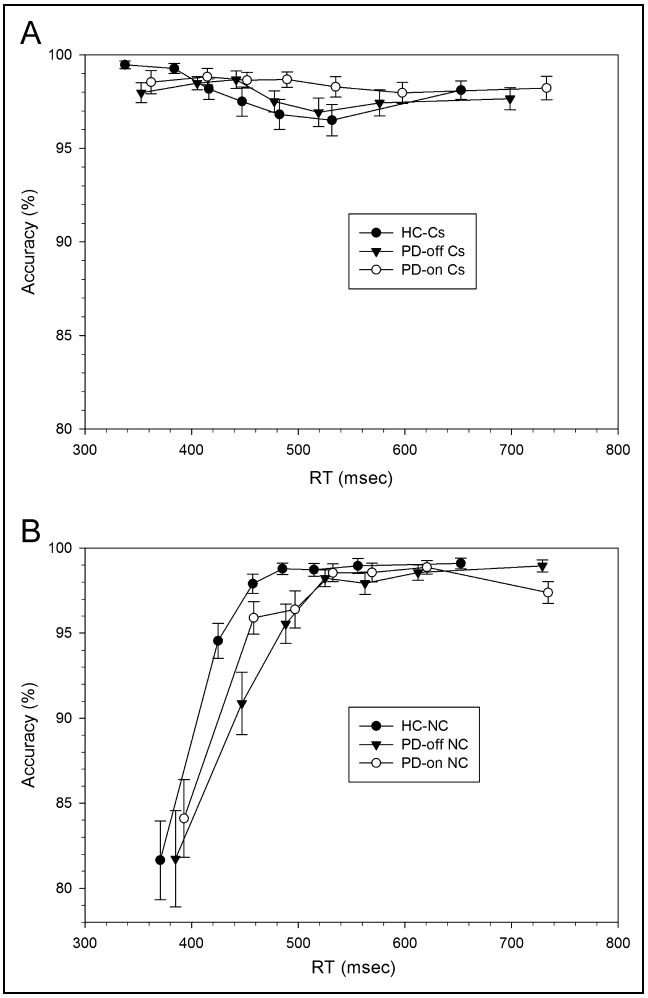

Figure 2. CAFs for corresponding (Cs) (A) and noncorresponding (Nc) trial (B) types for HCs and PD participants in the dopamine off and dopamine on state. Errors are predominantly associated with the fastest RTs on noncorresponding (Nc) trials, a pattern that does not differ between HCs and PD participants in the off dopamine state. Error bars reflect *SEM*s.

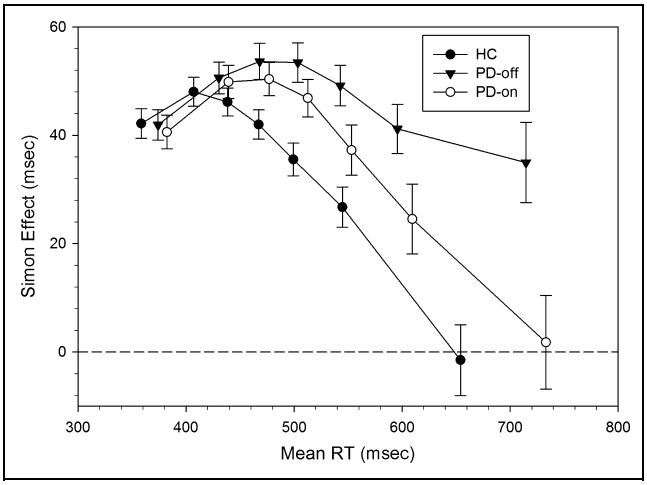

Figure 3. RT delta plots for HCs and PD participants in the dopamine off and dopamine on state. HCs show initial increase in interference followed by a drastic suppression of interference (i.e., large negative delta slope) at the slow end of the distribution. PD participants in off dopamine state show markedly less proficient suppression of interference from action impulses. The reduced proficiency of suppressing interference in the off dopamine state is significantly improved in the on dopamine state (i.e., a steeper negative-going delta slope at the slow end of the distribution). Error bars reflect *SEM*s.

report the interaction terms containing the Bins factor as the relationships between the Group and Correspondence factors remained, not surprisingly, consistent with the mean RT analyses described above. Consistent with our previous work, the delta plots in Figure 3 reveal variations in the size of the Simon effect across the RT distribution (Bins, $F(6, 104) = 11.59, p < .001$). As predicted by the DPAS model, the magnitude of the Simon effect produced by the initial activation of an incorrect action impulse was modulated by the hypothesized gradual buildup of inhibitory control, the result of which is a precipitous reduction in the Simon effect for the slowest RTs. The pattern of Simon effect modulation across the RT bins clearly differed between PD and HC groups (Group, $F(1, 109) = 8.91, p = .003$; Group × Bins, $F(6, 104) = 3.74, p = .002$). Whereas HCs showed a steep reduction of interference at slower latency bins, this interference reduction was much less effective among PD patients. The slope of the final segment of the delta plot was less negative-going for PD patients ($m = -0.05$, $SEM = .04$) compared with HCs ($m = -0$, $SEM = .03$) ($t(109) = 3.90, p = .001$, $BF_{01} = 0.007$). The estimated Bayes factor provides very strong evidence for the alternative hypothesis (that there is a difference between HC and PD off medication in the ability to suppress irrelevant information), that is, evidence for the alternative is 138 times stronger than for the null hypothesis.

According to the DPAS model, this suggests that PD patients withdrawn from their dopamine medications were less effective at inhibiting interference from action impulses compared with HCs.

Performance of PD Participants "Off" versus "On" Dopaminergic Medications

Mean Interference Effects on RT and Accuracy (Figure 1)

Overall, PD patients showed similar response latencies and accuracies in their withdrawn and active medication states (off vs. on: RT 526 vs. 535 msec; accuracy 96.5% vs. 97.2%) (Dopamine State: RT, $F(1, 52) = 1.31, p = .29$; accuracy, $F(1, 52) = 2.03, p = .16$). A robust Simon effect was produced across PD participants, which was revealed by reactions that averaged 40 msec slower and 3% less accurate for Nc compared with Cs trials (Correspondence: RT, $F(1, 52) = 181.16, p < .001$; accuracy, $F(1, 52) = 18.78, p < .001$). The magnitude of the Simon effect on RT was significantly reduced when PD patients performed in the active dopaminergic medication state (33 msec) compared with withdrawn from dopaminergic medication (47 msec), although the Simon effect costs to accuracy rates were similar between active (2.5%) and withdrawn states (2.9%) (Dopamine State × Correspondence: RT, $F(1, 52) = 10.07, p = .003$; accuracy, $F(1, 52) = 0.26, p = .61$) (Figure 1).

The three subgroups of PD patients showed similar overall response latencies and accuracies (levodopa monotherapy: 520 msec, 96.3%; agonist monotherapy: 556 msec, 97.6%; dual therapy: 516 msec, 96.6%) (PD Subgroup: RT, $F(2, 52) = 0.75, p = .48$; accuracy, $F(2, 52) = 0.44, p = .64$), that did not vary with dopaminergic medication state (PD Subgroup × Dopamine State: RT, $F(2, 52) = 0.26, p = .77$; accuracy, $F(2, 52) = 0.57, p = .57$). The subgroups showed similar overall magnitudes of the Simon effect on RT and accuracy rates (levodopa monotherapy: 46 msec, 3.7%; agonist monotherapy: 36 msec, 1.6%; dual therapy: 38 msec, 2.8%) (PD Subgroup × Correspondence: RT, $F(2, 52) = 1.14, p = .33$; accuracy, $F(2, 52) = 0.97, p = .38$) and Simon effects on RT and accuracy rates were similar across subgroups as a function of dopaminergic medication state (PD Subgroup × Correspondence × Dopamine State: RT, $F(2, 52) = 2.71, p = .08$; accuracy, $F(2, 52) = 0.08, p = .93$).

Response Capture by Incorrect Action Impulses (Figure 2A and B)

CAFs revealed a pattern of higher rates of fast errors on Nc compared with Cs trials at the early bins of the RT distribution, but similar high accuracy rates at intermediate and slower RT latency bins (Figure 2A and B). We first included all bins of the CAFs in the analysis (Bins factor) before focusing in on our primary comparison of accuracy rates at the fastest RT bin (i.e., to measure rates of fast, impulsive action errors). We again report the interaction terms containing the Bins factor, because the relationships between the Subgroup, Dopamine State, and Correspondence factors remained, not surprisingly, nonsignificant. The main effect of Correspondence was

significant again (Correspondence: $F(1, 52) = 18.26, p < .001$) and consistent with the mean accuracy analyses described above. Error rates varied across RT bins (Bins: $F(6, 47) = 6.67, p < .001$), and a clear difference was measured in the percentage of errors for Cs and Nc trials across bins of the RT distribution (Bins × Correspondence: $F(6, 47) = 6.41, p < .001$). On Nc trials, a pronounced pattern of fast errors was followed by a dramatic reduction in errors at intermediate and slow speeds. In contrast, the entire range of response latencies for Cs trials was associated with low error rates. Most importantly, the factors Subgroup and Dopamine State had no effect on these patterns of accuracy across the RT distribution (Subgroup × Bins: $F(12, 96) = 1.03$, $p = .43$; Dopamine State × Bins: $F(6, 47) = 1.34$, $p = .26$; Subgroup × Dopamine State × Bins: $F(12, 96) = .87$, $p = .58$; Subgroup × Correspondence × Bins: $F(12, 96) = .47$, $p = .93$; Dopamine State × Correspondence × Bins: $F(6, 47) = 2.04$, $p = .08$; Subgroup × Dopamine State × Correspondence × Bins: $F(12, 96) = .41$, $p = .96$). Even a focused analysis on the fastest bin of accuracy rates confirmed that the higher percentage of fast impulsive errors on Nc than on Cs trials (Correspondence, $F(1, 52) = 34.29, p < .001$) was unaffected by Subgroup and Dopamine State (Subgroup, $F(2, 52) = .62$, $p = .54$; Dopamine State, $F(1, 52) = 0.52$, $p = .47$; Subgroup × Correspondence, $F(2, 52) = .65$, $p = .52$; Dopamine State × Correspondence, $F(1, 52) = .58$, $p = .45$, $BF_{01} = 9.17$; Subgroup × Dopamine State, $F(2, 52) = 0.15$, $p = .86$; Subgroup × Dopamine State × Correspondence, $F(2, 52) = .02$, $p = .98$, $BF_{01} = 2518.9$).

Within the conceptual framework of the DPAS model, these results support the conclusion that the strength of impulse capture by incorrect responses was invariant across PD subgroups and dopaminergic medication states. This is also confirmed by the large Bayes factors supporting the null hypotheses that there is no effect of subgroups and medication state.

Suppressing Interference from Action Impulses (Figure 3)

We first included all bins of the delta plot in the analysis (Bins factor) before focusing on our primary comparison of the final delta plot slope (i.e., to measure proficiency of inhibitory control). We again report the interaction terms containing the Bins factor as the relationships between the PD Subgroup and Dopamine State factors remained, not surprisingly, consistent with the mean RT analyses described above. Once again, as predicted by the DPAS model, the delta plots revealed an increasing Simon effect at fast latency bins followed by a decreasing Simon effect at the slow end of the RT distribution congruent with the buildup of inhibitory control (Bins, $F(6, 47) = 12.87, p < .001$) (Figure 3). The pattern of Simon effect modulation across the RT bins differed between dopaminergic medication states (Dopamine State × Bins, $F(6, 47) = 3.53, p = .006$); in the on dopamine medication state, PD patients showed a much steeper reduction of interference compared with the off medication state. The Simon effect pattern across bins and the accompanying modulation of this pattern by dopaminergic medication state did not vary across PD Subgroups (PD Subgroups × Bins, $F(12, 96) = 1.68$, $p = .08$; PD Subgroups × Dopamine State × Bins, $F(6, 47) = 1.04$, $p = .42$). The slope of the final segment of the delta plot was more negative-going in the dopamine on medication state ($m = -.25$, $SEM = .05$) compared with the off medication state ($m = -.06$, $SEM = .05$) (Dopamine State, $F(1, 52) = 9.84$, $p = .003$, $BF_{01} = 0.16$), irrespective of PD Subgroup (PD Subgroup, $F(2, 52) = 2.27$, $p = .1$, $BF_{01} = 2.14$; Dopamine State × PD Subgroup, $F(2, 52) = 1.01$, $p = .37$, $BF_{01} = 2.71$). According to the DPAS model, these patterns confirm that PD patients were more effective at inhibiting interference from action impulses when on compared with withdrawn from dopaminergic medication. The Bayes factor further confirms that there is evidence for a substantial medication effect, that is, the evidence for the alternative is 6.3 times stronger than for the null. For the Subgroup effect and Subgroup with Dopamine State interaction effect, the Bayes factors indicate that there is substantial support for the null hypotheses, that is, no effect of Subgroup or Subgroup × Dopamine State interaction.

Performance of PD Patients "On" Dopamine Medications versus HCs

Mean Interference Effects on RT and Accuracy (Figure 1)

Overall, PD patients in their optimal medication state responded slower than HCs, but their accuracy rates were similar (PD vs. HC: RT, 531 vs. 482 msec; accuracy, 97.1% vs. 96.9%; Group: RT, $F(1, 109) = 9.33$, $p = .003$; accuracy, $F(1, 109) = 0.09$, $p = .77$). The Simon effect was again clearly present across PD on medication and HC; performance on Nc trials was 35 msec slower and 2% less accurate for Nc compared with Cs trials (Correspondence: RT, $F(1, 109) = 239.50$, $p < .001$; accuracy, $F(1, 109) = 63.31$, $p < .001$). PD patients on medication (36 msec) and HCs (34 msec) showed a similar Simon effect, both in terms of RTs as well as accuracy rates (PD: 2.7%; HC: 2.2%) (Group × Correspondence: RT, $F(1, 109) = .17$, $p = .68$; accuracy, $F(1, 109) = .69$, $p = .41$).

Response Capture by Incorrect Action Impulses (Figure 2A and B)

To avoid redundancy, we directly applied a focused analysis on the fastest bin of accuracy rates. No overall difference was found between the PD on and HC (Group, $F(1, 109) = .15$, $p = .70$, $BF_{01} = 5.8$). The analysis showed a higher percentage of fast impulsive errors on Nc compared with Cs trials (Correspondence, $F(1, 109) = 89.27$, $p < .001$), which

was similar across Groups (Group × Correspondence, $F(1, 109) = .91$, $p = .34$, $BF_{01} = 5.3$) (Figure 2A and B). Within the conceptual framework of the DPAS model, these results support the conclusion that the strength of capture by incorrect response impulses was similar across PD on medication and HC groups. The Bayes factor suggests that there is substantial evidence for the absence of a Group or Group × Correspondence effect; that is, there is respectively 5.8 and 5.3 times more evidence for the null than the alternative hypothesis.

Suppressing Interference from Action Impulses (Figure 3)

Again, the analysis is focused on the primary outcome measure, the slope of the final segment of the delta plot. The slope of the final segment of the delta plot was similar for PD patients on medication ($m = -.20$, $SEM = .05$) compared with HCs ($m = -.25$, $SEM = .03$) $t(109) = .77$, $p = .44$, $BF_{01} = 3.8$). According to the DPAS model, this suggests that medicated PD has the same ability to inhibit interference from action impulses compared with HCs. The Bayes factors suggest that there is substantial evidence for the absence of a Group effect; that is, there is 3.8 times more evidence for the null than the alternative hypothesis.

Dependence of Dopamine Effects on Baseline Inhibitory Control Performance

On the basis of the hypothesized inverted U-shaped association between dopamine levels and cognitive performance, we predicted that individuals with low baseline proficiency of inhibitory control (i.e., less negative final delta slope) in the off medication state would show improved inhibition under the influence of dopaminergic medication, whereas individuals with high baseline proficiency of inhibition in the off state would show no change or a reduction in inhibition in the active dopaminergic medication state. A significant negative correlation between initial value in the off state and the change value between off and on medication states ($r = -.58$; $p < .001$) suggested the possibility that high and low inhibition values in the off dopamine state were associated with reversed patterns of effects in the on dopamine state. It is tempting to interpret the strong correlation between initial value and change as an indication that effects of dopaminergic medication depend on individual baseline performances in the off medication state. However, there are two critical confounds that must be addressed: The initial value contributes to both variables, which artificially inflates the correlation, and the correlation may be influenced by regression to the mean (Tu & Gilthorpe, 2007). It is important to rule out these possible explanations, so we applied a conservative testing procedure that yields a more reliable test of the genuine relationship between initial value and change (Tu & Gilthorpe, 2007; Kelly & Price, 2005; Geenen & van de Vijver, 1993). If in fact poor suppressors benefit and good suppressors worsen on dopaminergic medication, it follows that the variance of the inhibition measure should be significantly different in the on and off medication states (see Myrtek & Foerster, 1986). The test of the equality of variances between the two conditions (Tu & Gilthorpe, 2007; Kelly & Price, 2005) revealed that the variances of the suppression measure in the on and off medication states did not differ ($t(53) = -.86$, $p = .40$, $BF_{01} = 6.59$), which is further supported by the Bayes factor, indicating substantial evidence for the null hypothesis. Thus, we are unable to rule out the role of alternative influences on the measured association between initial and change values. This set of additional analyses reduces confidence that the observed dopaminergic effects on inhibition are driven by individual baseline differences in the dopamine withdrawn state.

Association of PD Clinical Features to Performance Measures

Correlational analyses focused on the association between key clinical features (e.g., disease duration, total LEDD, motor UPDRS scores off medication states, depression ratings, MOCA scores, and QUIP scores) and both the strength of impulse capture (i.e., fast errors) and the proficiency of inhibition (i.e., final delta slope) during off dopaminergic medication state. Consistent with many reports in the literature, none of these measures was associated with the performance measures (all ps $> .09$). This suggests that specific cognitive control processes measured experimentally capture a unique aspect of the disease unrelated to the very broad measures of the clinical presentation of PD.

DISCUSSION

The Simon task provided a direct measure of interference costs in times of response conflict. On average, reactions were slower and less accurate on noncorresponding compared with corresponding trials, suggesting that the simultaneous activation of a conflicting response impulses on noncorresponding trials interfered with the efficiency of selecting the desired action. Using the DPAS analytical framework, distributional analyses confirmed two dissociable effects of conflicting responses on performance that were not disclosed by mean results. First, CAFs showed that errors on noncorresponding trials were predominantly associated with the fastest RTs, suggesting that errors were impulsive reactions driven by the initial activation of the conflicting response. Second, when participants did not commit impulsive errors, the activation of the conflicting response produced a pattern of increasing interference costs across fast and intermediate response latencies that then reversed drastically at the slower end of the RT distribution. According to the DPAS model, this

dramatic reversal and reduction of interference costs result from the gradual buildup of inhibitory control upon detecting response conflict, which is most potent on slow latency response trials (see discussion by van den Wildenberg et al., 2010). These patterns replicate several previous studies, thus setting the stage for evaluating the effects of the severely depleted dopamine system in PD and restorative dopamine therapies on the strength of impulse capture by conflicting action impulses and the proficiency of inhibitory control engaged to suppress interference from these impulses.

Effects of PD and Dopamine on Impulse Capture

Prior studies have investigated PD effects on the expression and suppression of action impulses using the DPAS framework while patients were taking their dopaminergic medication, that is, in the "on" medication state (van Wouwe et al., 2014; Wylie et al., 2009a, 2009b, 2010). Studies of PD patients in the "on" state have not demonstrated increased impulse capture compared with HCs, but these studies have left open the question as to whether dopaminergic medications modulate impulse capture. The current findings extend this work by showing that PD patients withdrawn from their dopaminergic medications (i.e., in the "off" state) do not experience deficits in impulse capture. The Bayes factor provided additional confidence in these findings by indicating that there is substantial evidence for this null effect. Thus, the severe dopamine depletion in PD does not generally increase susceptibility to acting on initial action impulses (i.e., fast, impulsive errors revealed by CAFs). Moreover, the current data confirm that drugs that replenish dopaminergic activity have little effect on susceptibility to impulse capture. The patterns of fast impulsive errors neither varied by the medication state (i.e., on vs. off dopaminergic therapy) nor by the type of dopaminergic therapy prescribed (e.g., levodopa, agonist, levodopa + agonist). A prior study (Wylie et al., 2012) of PD patients withdrawn from or actively taking their prescribed dopamine agonist medication, but who remained on their levodopa medication, reported similarly that dopamine agonist state did not modulate impulse capture. In fact, in this study, patients who developed clinically defined impulse control disorder (e.g., pathological gambling, compulsive buying, hypersexuality) on their dopamine agonist medication showed reduced as opposed to exacerbated strength of impulse capture. Together, these patterns and replicated findings argue against a predominant role of dopamine in the initial gating of impulsive motor actions in PD.

The absence of dopaminergic modulation of the initial gating of impulsive actions concords with recent studies of PD and healthy adults showing that dopamine medication as well as genetic differences in key dopamine polymorphisms (e.g., COMT, DRD2, DAT1, DRD4) do not influence rates of commission errors in a standard go/no-go disjunctive reaction task (Gurvich & Rossell, 2014; Mulligan, Kristjansson, Reiersen, Parra, & Anokhin, 2014; Farid et al., 2009). Similar to impulsive reaction errors on the Simon task, commission errors on the classic go/no-go disjunctive reaction task are typically fast reactions on no-go trials, suggesting poor initial gating (i.e., restraint) of strong prepotent actions. Taken together, these findings indicate that the dopamine system plays a limited role in processes governing an individual's gating or susceptibility to initial capture by strong impulsive action tendencies.

Two mentionable exceptions have been described in the PD literature. PD patients with predominant postural instability and gait symptoms show stronger impulse capture than patients with predominant tremor symptoms (Vandenbossche et al., 2012). Thus, there may be a particular subtype of PD symptoms that are linked to alterations in the initial gating of impulsive action tendencies. Consistent with this idea, accruing evidence shows that PD patients with freezing of gait symptoms show greater difficulty resolving response conflict, although no studies have used the DPAS analytical framework to separate impulse capture from the proficiency of inhibitory control. Interestingly, the postural instability and freezing of gait symptoms are typically among the least responsive to dopaminergic medications, which also indirectly hints at a nondopaminergic process involved in poor motor impulse control (Vandenbossche et al., 2012). Second, deep brain stimulation of subthalamic nuclei may also induce increases in impulse capture and other forms of impulsive action errors (Jahanshahi, 2013; Cavanagh et al., 2011; Hershey et al., 2010; Wylie et al., 2010). Thus, there may be a specific circuitry in the BG, such as the hyperdirect pathway, that when modulated has a direct impact on the gating of initial action impulses. A recent theoretical model of freezing of gait also asserts a central role for abnormal subthalamic nucleus function in the freezing of gait phenomenon (Lewis & Shine, 2016; Nutt et al., 2011). These studies indicate that BG circuitries inclusive of the subthalamic nucleus may be key to modulating the gating of impulsive motor actions.

Effects of PD and Dopamine on Selective Response Inhibition

Although the initial gating of impulsive action tendencies does not appear to be modulated by dopamine depletions in PD or by dopaminergic therapy, the reactive engagement of cognitive control processes to inhibit conflicting response impulses appears directly impacted by dopamine depletions in PD and dopaminergic medications. Prior studies of PD patients actively taking their dopaminergic medications have revealed a consistent deficit in the proficiency of inhibitory control of conflicting response impulses (i.e., a less steep inhibition slope in delta plots) compared with HCs (van Wouwe et al., 2014; Wylie et al., 2009a, 2009b, 2010). Again, the potential modulatory role of dopamine in these studies remained

uncertain. Our findings that a large sample of PD patients withdrawn from their dopaminergic medications show significantly reduced proficiency of inhibitory control replicates and extends prior findings of medicated PD patients and the recent study showing selective reduction of inhibitory control, but no changes in impulse capture, among healthy adults in a dopamine precursor depleted state (Ramdani et al., 2015). PD very clearly has a disruptive effect on the ability to inhibit the interference produced by an action impulse that conflicts with a desired action. That this effect is dopamine dependent is further supported by our data showing a drastic improvement of inhibitory control when these same PD patients are actively taking their prescribed dopaminergic medications, irrespective of the type of dopaminergic therapy prescribed (i.e., levodopa, agonist, levodopa + agonist). The Bayes factors provided additional confidence in these findings by indicating that there is very strong evidence for these effects.

In a previous study, we reported that PD patients prescribed agonist medication, who performed the Simon task withdrawn and actively taking their agonist medication, showed reduced inhibitory control on compared with withdrawn from their medication (Wylie et al., 2012). So what might explain the apparent discrepancy with the current patterns? There were some important differences in the former study. First, all patients were taking agonist medication. Second, the majority of patients in that study was also taking a dopamine precursor and remained on the precursor during performance (i.e., only the agonist medication was withdrawn), and thus, patients were not completely withdrawn from dopamine modifying medications. However, how PD patients performed off of their dopamine agonist determined the direction of the agonist effect on their inhibitory control. Here we attempted a replication of this pattern of baseline-dependent effects in patients withdrawn from all dopaminergic medications, and although the overall pattern was suggestive of baseline effects, we could not fully rule out explanations invoking regression to the mean or the artificial correlation related to using the initial change value twice. Thus, when considering all dopaminergic medications together, we could not find clear evidence consistent with the notion that circuitry implementing this form of inhibitory action control is in part governed by an inverted U-shaped dopamine–performance curve in which poor inhibition benefits from increasing dopamine in the brain and more efficient inhibition remains the same or is degraded by additional dopamine. The possibility that the inverted U-shaped curve applies to a more fine-grained interaction between levodopa and agonist medication could not be directly addressed in the current study, but certainly warrants future attention. Thus, based on the current findings, inhibitory control of action impulses is not easily reconciled with a similar dopamine–performance curve observed in studies of working memory, probabilistic learning, and other cognitive control processes (Costa et al., 2014; Cools & D'Esposito, 2011; Cools, Barker, Sahakian, & Robbins, 2001; Swainson et al., 2000; Gotham, Brown, & Marsden, 1988). However, our behavioral findings allow limited interpretation, and PET imaging would be required to provide more conclusive statements about the relation between individual differences in baseline DA and inhibitory control.

A role for dopamine in reactive inhibitory control processes is consistent with most other work (but see George et al., 2013, who did not find an improvement in inhibitory control with dopamine in PD) linking variations in dopamine activity to the proficiency of inhibiting initiated actions in a stop-signal paradigm (also referred to as action cancellation). For example, imaging studies show that dopamine release and dopamine receptor availability predict individual differences in reactive inhibitory control processes (Albrecht, Kareken, Christian, Dzemidzic, & Yoder, 2014; Ghahremani et al., 2012). Moreover, genetic variations in dopamine transporter genes and COMT also vary with inhibitory control in the stop-signal paradigm (Cummins et al., 2012; Congdon, Constable, Lesch, & Canli, 2009). Similarly, higher spontaneous eye blink rate, which is a putative marker of dopamine system integrity, correlates with faster inhibitory control in the stop-signal task (Colzato, van den Wildenberg, van Wouwe, Pannebakker, & Hommel, 2009). Together, a picture is emerging linking dopamine directly to reactive inhibitory control processes, particularly in times of response system conflict.

Study Limitations and Extant Issues

There are a few limitations and extant issues worth discussing. We measured the effects of temporary withdrawal from dopaminergic medications, and although there were clear effects of dopaminergic medication on inhibitory control, it remains an open question how longer washout periods may have influenced performance. It is also well known that chronic dopaminergic medication use leads to changes in dopamine receptor density and sensitivity (LeWitt, 2015; Riverol et al., 2014), so these effects cannot be fully appreciated in the current study. Ideally, this could be investigated by tracking changes in impulse capture and inhibitory control longitudinally in drug naive (de novo) patients who initiate dopaminergic therapy (Vriend et al., 2015).

Measures of impulse capture and the proficiency of inhibition did not correlate with variables reflecting broad characteristics of clinical PD, including disease duration, motor symptom severity, gross cognitive status, impulsive-compulsive behavior ratings, and total levodopa equivalent dose. This is commonly found in the reported literature and likely reflects differences in the levels of analysis (e.g., millisecond precision vs. subjective clinical judgment ratings and terse cognitive measures) as well as heterogeneity in the pattern and course of PD motor and

cognitive symptoms and their response to medication. The search for genetic and imaging biomarkers of dopamine and BG integrity that closely correspond to variations in impulse control and the proficiency of inhibitory control in PD represents a critical enterprise for future investigations.

Conclusion

The current findings show that dopamine depletion in PD and therapies designed to replenish dopamine function have minimal impact on the initial gating or capture by stimulus-driven action impulses but directly modulate the proficiency of reactive inhibitory control engaged to suppress these impulses.

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Reprint requests should be sent to Nelleke C. van Wouwe, Department of Neurology, Vanderbilt University Medical Center, 1161 21st Avenue South, A-0118 Medical Center North, Nashville, TN 37232, or via e-mail: nelleke.van.wouwe@vanderbilt.edu.

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