Dopamine Agonists and the Suppression of Impulsive Motor Actions in Parkinson Disease

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Abstract

■ The suppression of spontaneous motor impulses is an essential facet of cognitive control that is linked to frontal-BG circuitry. BG dysfunction caused by Parkinson disease (PD) disrupts the proficiency of action suppression, but how pharmacotherapy for PD impacts impulsive motor control is poorly understood. Dopamine agonists improve motor symptoms of PD but can also provoke impulsive–compulsive behaviors (ICB). We investigated whether dopamine agonist medication has a beneficial or detrimental effect on impulsive action control in 38 PD patients, half of whom had current ICB. Participants performed the Simon conflict task, which measures susceptibility to acting on spontaneous action impulses as well as the proficiency of suppressing these impulses. Compared with an off-agonist state, patients on their agonists were no more susceptible to reacting impulsively but were less proficient at suppressing the interference from the activation of impulsive actions. Importantly, agonist effects depended on baseline performance in the off-agonist state; more proficient suppressors off agonist experienced a reduction in suppression on agonist, whereas less-proficient suppressors off agonist showed improved suppression on agonist. Patients with active ICB were actually less susceptible to making fast, impulsive response errors than patients without ICB, suggesting that behavioral problems in this subset of patients may be less related to impulsivity in motor control. Our findings provide further evidence that dopamine agonist medication impacts specific cognitive control processes and that the direction of its effects depends on individual differences in performance off medication. ■

INTRODUCTION

Reacting spontaneously to external events is an ineludible challenge in a constantly changing environment. Spontaneous reactions to stimulus events can be impulsive (e.g., a driver slamming on her brakes to avoid being hit by a car that has run a red light) or highly overlearned (e.g., a driver slamming on her brakes to avoid running a red light). In many situations, spontaneous actions are advantageous, particularly if a swift action leads to reward or averts a negative consequence. However, action impulses sometimes conflict with optimal or goal-directed behavior. The cognitive neuroscience of action control has attracted considerable attention in recent years. This work has highlighted the role of frontal-BG circuitry as an important interface for selecting and inhibiting impulsive actions (for a review, see Ridderinkhof, Forstmann, Wylie, Burle, & van den Wildenberg, 2011). Consistent with this view, many neuropsychiatric (e.g., schizophrenia and obsessive–compulsive disorder) and neurological disorders (Parkinson disease [PD], Huntington disease, and Tourette syndrome) associated with frontal-BG

dysfunction have been linked with various forms of suboptimal impulsive behavior (Frank, Piedad, Richards, & Cavanna, 2011; Kaladjian, Jeanningros, Azorin, Anton, & Mazzola-Pomietto, 2011; van den Heuvel et al., 2010; Voon & Fox, 2007; Grant, Mancebo, Pinto, Eisen, & Rasmussen, 2006). An important aspect of this research is determining how treatments for these conditions affect the expression and control of impulsive actions. The current study extends this work in PD by examining the effects of dopamine agonist treatment on impulsive action control and how these effects are driven by individual differences between patients.

PD Pharmacotherapy and Action Control

The cardinal clinical features of PD—bradykinesia, rigidity, and tremor—are attributed largely to the neurodegeneration of the dopamine-producing substantia nigra pars compacta neurons of the BG (Bjorklund & Dunnett, 2007; McAuley, 2003). In addition to playing a key role in rudimentary motor control functions, the BG, via elaborate interconnections with prefrontal cortices, are increasingly recognized as vital nodes in complex cognitive and motor control networks involved in action selection and suppression (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004; Redgrave,

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Prescott, & Gurney, 1999; Hikosaka, 1998; Mink, 1996; Mink & Thach, 1993; Robbins & Brown, 1990; Alexander, DeLong, & Strick, 1986). Empirical support for this role is bolstered by functional imaging studies that reveal BG activity associated with action control functions (e.g., action suppression) and by studies in which PD patients have been found to be less proficient in action control than healthy age-peers (Aron, 2007; Gauggel, Rieger, & Feghoff, 2004; Praamstra, Stegeman, Cools, & Horstink, 1998). Although the dopamine precursor, levodopa, remains the gold standard of dopaminergic treatment in PD, dopamine agonists are frequently used to reduce clinical motor symptoms in patients who do not tolerate levodopa, develop a suboptimal response to it, or decide to delay its use in treatment to avert unwanted side effects (e.g., levodopa-induced dyskinesia; Parkinson Study Group, 2000; Rascol et al., 2000). Despite their widespread clinical use, the impact of dopamine agonists on action control processes in PD patients has been relatively unexamined. The first aim of the current investigation was to study the effect of dopamine agonist administration on the ability of PD patients to suppress or inhibit the expression of action impulses that interfere with the execution of goal-directed behavior.

The importance of understanding the effects of dopamine agonists on inhibitory action control processes is underscored by at least two key considerations. First, previous studies have shown that the capacity of PD patients to suppress incorrect, prepotent action impulses is diminished (Wylie et al., 2009a, 2009b; Praamstra, Plat, Meyer, & Horstink, 1999). This reduction in action suppression has been demonstrated in separate studies of patients who were either under the influence of their dopamine replacement medications or temporarily withdrawn from their dopamine medications. Thus, although a deficit in inhibitory action control appears to be an important feature of PD, it remains unclear whether dopamine medications, including dopamine agonists, improve, worsen, or have no effect on inhibitory control processes within or across individuals.

The possibility that dopamine agonists may actually worsen the proficiency of inhibitory action control among PD patients is suggested by the second consideration that has emerged from the clinical literature. A subset of patients who are being treated with these agents develops uncharacteristic and often destructive behavioral changes that are expressed in impulsive decision-making (e.g., making an impromptu automobile purchase that depletes a retirement savings account) and/or difficulties controlling compulsive behaviors (e.g., spending entire days performing a hobby while neglecting to pay bills; Voon & Fox, 2007; Dodd et al., 2005). These so-called impulsive–compulsive behaviors (ICB) are evoked by agonists in approximately 15–20% of PD patients and are thought to involve changes in a variety of underlying processes such as behavioral inhibition, reward anticipation, and biases in decision-making under risk (Claassen et al., 2011; Ye, Hammer, Camara, & Munte, 2011; Housden,

O'Sullivan, Joyce, Lees, & Roiser, 2010; Weintraub et al., 2010; Voon et al., 2006). Hypotheses concerning these changes are driven largely by the known affinity of dopamine agonists for D2/D3 dopamine receptor types that are highly represented along mesocorticolimbic dopamine reward pathways (Black et al., 2002). In fact, recent studies have revealed important differences in performance on reward and risk processing tasks between PD patients who do and do not develop ICB while taking agonists (Claassen et al., 2011; Voon et al., 2011; van Eimeren et al., 2010). Notably, there is no current direct evidence that these patients experience a reduction in inhibitory control over motor actions. Thus, an important second aim of the current study was to compare the effects of dopamine agonist medication on inhibitory action control among PD patients with active impulsive–compulsive symptoms and patients who have not developed these symptoms while taking dopamine agonists.

Measuring the Expression and Suppression of Action Impulses

The well-known Simon task (Simon, 1969, 1990) and the dual process activation–suppression (DPAS) model (Ridderinkhof, 2002a, 2002b; Kornblum, Hasbroucq, & Osman, 1990) provide a powerful experimental and conceptual framework for investigating the expression and suppression of action impulses. In the well-known Simon task, selecting a designated action based on some physical attribute of a stimulus (e.g., its color) is influenced by two streams of processing: one encompassing a relatively fast, spontaneous activation of an action impulse triggered by the location of the stimulus and the other encompassing a relatively slower, deliberate translation of the goal-directed stimulus feature (color) into the designated action (see Figure 1). When these two streams correspond (e.g., the color of a circle appearing in the left hemifield signals a left-hand response), the simultaneous or dual process engagement of the same action yields fast RTs and high accuracy rates. Conversely, RT slows and accuracy rates decrease when the action signaled by the circle's color and the action impulse triggered by its spatial location are non-corresponding (e.g., the color of a circle appearing in the right hemi-field signals a left-hand response), presumably reflecting the extra time required to suppress the interfering action impulse. This effect has been used with considerable success to study individual and group differences in cognitive control over interfering action impulses (Hommel, 2011; van den Wildenberg et al., 2010).

The DPAS model specifies an analytical framework for dissociating two essential and temporally distinct cognitive processes that are masked in analyses of mean Simon effects. The first process, henceforth referred to as *impulse capture*, is assumed to occur very shortly after the onset of the imperative stimulus and to reflect the degree to which an individual's response system is susceptible to capture by the activation of the location-driven action impulse. The
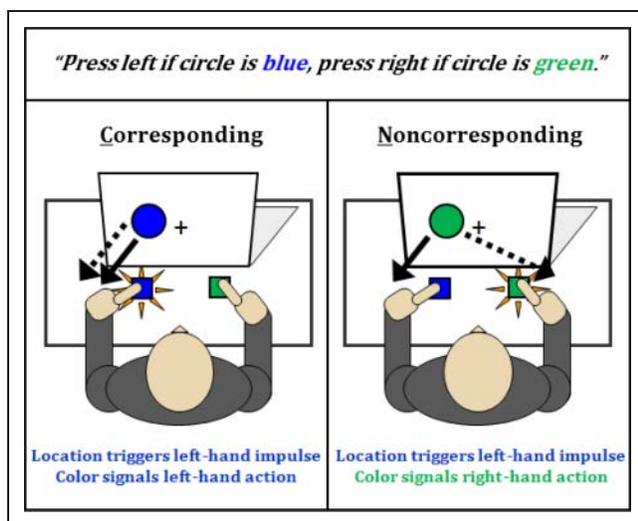
Figure 1. Instructions and example of trial types in the Simon task. Left shows Cs trials in which an initial response impulse signaled by the goal-irrelevant location of a stimulus corresponds to the same action signaled by the goal-relevant color feature of the stimulus; this facilitates RT and accuracy. Right depicts Nc trials in which the stimulus location activates an action impulse that conflicts with the correct action signaled by the stimulus color, which produces impulsive response errors and RT interference on correct trials. The detrimental influence of location-driven response impulses on the RTs and accuracy rates of Nc trials relative to the facilitative influence on Cs trials is called the Simon effect.

strength of impulse capture is reflected in the proportion of fast, impulsive errors evident in plots of accuracy rates against RT (i.e., a conditional accuracy function [CAF]; van den Wildenberg et al., 2010; Wylie, Ridderinkhof, Bashore, & van den Wildenberg, 2010; Kornblum et al., 1990). The second process is assumed to reflect top–down inhibitory control that is engaged more slowly and builds up to suppress the interference induced by an incorrect action impulse (Ridderinkhof, 2002a). 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 emerge after it has been triggered by the incorrect action impulse. Plotting the magnitude of the Simon interference effect 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 prepotent motor impulses.[1] Empirical support for this assertion comes from several studies using both nonclinical and clinical populations (Wylie et al., 2009b, 2010a, b; 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, Wylie, & van den Wildenberg, 2011).

The Current Study

The aims of the study were to determine how the expression and suppression of impulsive motor actions among PD patients are (i) affected by dopamine agonist medication and (ii) differentially altered in individuals with current ICB. Patients with and without agonist-induced ICB completed the Simon task on two occasions, once under the influence of their agonist medications and once after being withdrawn from it temporarily. In our primary analyses, we tested two competing hypotheses. First, if the effects of dopamine agonists on the cognitive control over actions are ameliorative, patients should show more proficient suppression of incorrect action impulses (i.e., less impulsive errors and a reduced Simon effect). If, however, agonists impair cognitive control and predispose to ICBs, this predisposition should manifest itself through an increased commission of impulsive action errors (i.e., stronger impulse capture) and/or a reduced proficiency in suppressing interference from impulsive action tendencies. This pattern should be more pronounced among patients with active ICB than among patients who do not have these symptoms. In a secondary analysis, we studied the association of agonist dosage on the expression and suppression of action impulses. Last, we completed a third set of analyses inspired by growing evidence, which suggests that cognitive effects of dopamine medication may depend on baseline cognitive performance (Cools & D'Esposito, 2011). Specifically, patients who perform proficiently while off their dopamine medications may show a decline in performance while on their dopamine medications, whereas patients who perform poorly while off their medications may show an improvement in performance while on their medications. If this differential pattern is demonstrated, it would suggest that treatment decisions may enhance or diminish cognitive control depending on interindividual variation in baseline performance levels.

METHODS

Participants

Thirty-eight individuals with idiopathic PD participated in this study, all of whom were recruited from the patient population in the Movement Disorders Clinics at the University of Virginia and Vanderbilt University. They all met the following inclusion criteria: no history of (i) other neurological condition besides PD; (ii) bipolar affective disorder, schizophrenia, or other psychiatric condition known to compromise executive cognitive functions; or (iii) untreated or unstable mood disorder or medical condition known to interfere with cognition (e.g., diabetes, pulmonary disease). Participants were evaluated and diagnosed with idiopathic PD by a movement disorder neurologist, were being treated with the dopamine agonists pramipexole or ropinorole, and performed at a level on the Mini Mental Status Examination (Folstein, Folstein, & McHugh, 1975) that revealed no evidence of dementia

(all scores > 25). The severity of their motor symptoms was graded using the Unified Parkinson Disease Rating Scale motor subscore; additionally, they all received a Stage III rating or less using the Hoehn and Yahr scale (Hoehn & Yahr, 1967). On the basis of rating scale scores and neurological evaluation, each patient was considered to be experiencing mild to early moderate disease presentation. In addition to being treated with dopamine agonist medication to control their motor symptoms, 23 of the 38 patients were receiving levodopa cotherapy. The remaining 15 patients were prescribed agonist monotherapy. All of the patients showed a positive medication response (i.e., a clinically observed reduction in motor symptoms). Dosages for the dopamine medications were converted to levodopa equivalent daily dose (LEDD) values (Weintraub et al., 2006). Six patients were also being treated with antidepressant medication. These patients, as well as the other participants, reported stable mood functioning. They all denied symptoms associated with major depression, both during the clinical interview and when they completed the experimental portions of the study. 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 the authors' institutions. Thirty-four of these patients completed additional cognitive tasks that are reported elsewhere (Claassen et al., 2011). The demographic characteristics of the participants in the current study are listed in Table 1.

Patients were also classified with respect to the emergence of ICB coincident with dopamine agonist treatment. First, patients and their spouses/caregivers completed the self and informant screening versions of the Questionnaire for Impulsive–Compulsive Symptoms in Parkinson Disease that screens for the presence of any of several ICBs related to gambling, buying, sexual behavior, eating,

hobbyism, punding, or medication use (Weintraub et al., 2009). A follow-up clinical interview firmly established the presence or absence of any ICBs, coincidence of ICBs with initiation of agonist pharmacotherapy, and the disruptive impact of these behaviors on daily functioning according to established criteria (Weintraub et al., 2009; Voon et al., 2006; Weintraub & Potenza, 2006). Patients were assigned to the ICB group if they were experiencing at least one of these behaviors, and patients who were not included in this group reported no such behaviors and did not meet criteria for ICB. The sample of ICB patients presented with compulsive gambling (16%), compulsive buying/shopping (53%), hypersexuality (53%), compulsive eating (42%), and compulsive hobbyism (68%). All but one patient presented with two or more ICBs.

Importantly, participants with ICB completed the study before withdrawing from or decreasing their agonist medications; thus, they performed the study while presenting with active ICB. After study completion, follow-up neurological visits confirmed that all patients with ICB showed a marked decline in ICB coincident with discontinuation or reduction of agonist medication. We recruited equal numbers of patients in both groups ($n = 19$), each of whom completed two test sessions that took place on two separate visits. On one visit, they were tested while taking all of their dopamine-enhancing medications and were in the optimal "on" phase of their medication cycle. On the other visit, they completed testing after an 18–24 hr withdrawal from their dopamine agonist medications. The order of visits was counterbalanced across participants. Patients on levodopa cotherapy were not withdrawn from this medication at either visit. Importantly, no changes in levodopa or agonist dosages or addition or discontinuation of either drug for clinical purposes were made at any time during study participation. As depicted in Table 1, the subgroups displayed similar disease characteristics.

Table 1. Sample Characteristics

| | All Patients | ICB Subgroups | | p |
		ICB	No ICB	
Sample size	38	19	19	
Age (years)	62.1 (7.0)	60.9 (5.6)	63.2 (8.1)	>.10
Sex (M:F)	19:19	10:9	9:10	>.10
Education (years)	16.6 (2.6)	16.8 (2.3)	16.4 (2.9)	>.10
MMSE	28.8 (1.5)	28.8 (1.5)	28.8 (1.5)	>.10
Disease duration (years)	7.6 (5.9)	9.4 (6.8)	5.9 (4.3)	.06
UPDRS motor score	16.8 (8.1)	18.4 (7.4)	15.3 (8.6)	>.10
Agonist LEDD (mg)	247 (138)	277 (145)	218 (128)	>.10
Agonist duration (years)	3.7 (3.6)	4.6 (4.0)	2.8 (2.9)	>.10
Daily levodopa (mg)	-	584 (270; $n = 13$)	618 (220; $n = 10$)	>.10

MMSE = Mini Mental Status Examination; UPDRS = Unified Parkinson Disease Rating Scale; M = male; F = female.

Task and Procedures

The Simon task was administered using an IBM-compatible computer and a 17-in. monitor located at eye level approximately 1 m in front of the participant. Participants were seated comfortably and grasped a handheld response grip in each hand that registered responses via a left or right thumb press made on a button at the end of each grip. They completed four blocks of 60 experimental trials that were preceded by a block of 60 practice trials. The beginning of a block of trials was signaled by the appearance of a small black, square-shaped fixation mark in the center of a light gray background on the computer screen. It remained on the screen for the entire duration of the block of trials. Within a variable duration of 1750–2250 msec following the initial appearance of the fixation mark, 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 either the participant made a response or a 1500-msec time limit elapsed. Another variable interval of 1750–2250 msec passed following a response or expiration of the time limit 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. It took approximately 3–4 min to complete a 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. Participants were encouraged to maintain their gaze on the fixation mark because it helped them sustain their attention and to try to respond as quickly as they could while maintaining a high level of accuracy (90–95%).

To elicit the Simon effect, two trial types were configured to manipulate the correspondence between the spatial location of the circle and the response signaled by its color (see Figure 1). 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 120 Cs and 120 Nc trials.

Statistical Techniques

Data outliers were addressed using methods described previously (Wylie, Ridderinkhof, Bashore, et al., 2010). Mean RT and square-root transformed accuracy data were submitted to separate repeated-measures ANOVAs. The within-subject experimental factors in the initial analysis were Correspondence (corresponding, noncorresponding) and Agonist (off, on), with a between-subject factor of ICBs (present, absent).

The strength of response capture by incorrect action impulses was inferred from the proportion of fast errors revealed in CAFs that plot accuracy rates as a function of the entire RT distribution for each level of correspondence. Accuracy rates for the fastest RT bin of the CAFs have been demonstrated to be the most sensitive measure of capture (van den Wildenberg et al., 2010). The proficiency of suppression was inferred from delta plots, which plot the Simon effect (i.e., mean RT for the noncorresponding condition minus mean RT for the corresponding condition) as a function of RT. The slope between the delta values of the two slowest RT bins was the primary dependent measure because this value has been demonstrated to be the most sensitive measure of the proficiency of inhibitory control over action impulses and associated with systematic differences in the activation of prefrontal areas (e.g., right inferior frontal cortex), which have been linked empirically to inhibitory action control and have known projections to BG structures (Davelaar, 2008; Forstmann, Jahfari, et al., 2008; Forstmann, van den Wildenberg, & Ridderinkhof, 2008; Ridderinkhof, 2002a; for a review, see van den Wildenberg et al., 2010).

The aforementioned values derived from the CAFs and the delta plots were then submitted to separate repeated measures ANOVAs to examine factor effects on the expression and suppression of action impulses, respectively. Our detailed methods for computing and analyzing CAFs and delta plots derived from the Simon task can be found elsewhere (van den Wildenberg et al., 2010; Wylie, Ridderinkhof, Bashore, et al., 2010; Wylie, Ridderinkhof, Elias, et al., 2010). Pearson correlations were computed to test associations between agonist dosage and key performance variables. Statistical techniques were also used to assess the impact of baseline inhibitory control performance in the off medication state on the effects of performance in the on-agonist state. These techniques tested the alternative explanation of baseline effects in terms of regression to the mean.

Patients prescribed with levodopa cotherapy took their levodopa medications as usual during on and off dopamine agonist testing sessions. Thus, in the off-agonist state, some patients performed under the acute influence of levodopa, and patients prescribed with agonist monotherapy performed the off-agonist session completely withdrawn from dopamine-modifying medications. To determine the effect of levodopa status on performance variables and its potential interaction with agonist state, we re-analyzed mean and distributional data with the factor levodopa (none, present) included as a between-subject variable. As the presence or absence of levodopa did not influence the pattern of results, we present data that collapse across levodopa status (see analyses in Supplementary Material).

RESULTS

Table 1 lists overall patient characteristics as well as characteristics for subgroups based on the presence or absence of ICB. Notably, these subgroups did not differ in any of the listed clinical features; the only exception was a trend toward longer disease duration among patients presenting with ICB compared with those without ICB. We next present the results from the Simon task.

Dopamine Agonist Medication and ICBs

Mean Interference Effects on RT and Accuracy

It is apparent in Figure 2A that the mean response latencies and accuracy rates of PD patients were unaffected by their dopamine agonist medication state (on vs. off: RT, 483 vs. 478 msec; accuracy, 96.2% vs. 95.3%; agonist: RT, $F(1, 36) = 0.14$, $p = .71$; accuracy, $F(1, 36) = 1.58$, $p = .22$). Similarly, as depicted in the top of Figure 2B and 2C, a robust Simon effect was produced among these participants on RT (40 msec; correspondence: $F(1, 36) = 128.27$, $p < .001$) that was unaffected by agonist state (on: 40 msec, off: 41 msec; Agonist × Correspondence: $F(1, 36) = 0.06$, $p = .81$). Varying somewhat from this pattern, as illustrated in the bottom of Figure 2B and 2C, the strong Simon effect on accuracy (−3%; correspondence: $F(1, 36) = 27.26$, $p < .001$) tended to increase when patients were off-agonist medication (on: −2.3%, off: −3.4%; Agonist × Correspondence: $F(1, 36) = 3.42$, $p = .07$). Overall, treatment with a dopamine agonist had no effect on mean response latency and accuracy and had minimal, if any, influence on the Simon effect.

In Figure 3A, it can be seen that, although the presence or absence of ICB had no influence on overall mean RT (present: 473 msec, absent: 488 msec), patients with these symptoms did tend to have higher overall mean accuracy rates (97.2% vs. 94.3%; ICB: RT, $F(1, 36) = 0.52$, $p = .47$; accuracy, $F(1, 36) = 3.54$, $p = .07$); and, as shown in Figure 3C, these patterns were not altered by agonist state (ICB × Agonist: RT, $F(1, 36) = 0.00$, $p = .96$; accuracy, $F(1, 36) = 2.51$, $p = .12$). Similarly, the magnitude of the Simon effect on accuracy, depicted in Figure 3B, was not related to the presence of ICB (present: −2.1%, absent: −3.6%), whereas the effect tended to be reduced on RT among patients who were symptomatic (present: 34 msec vs. absent: 47 msec; ICB × Correspondence: RT, $F(1, 36) = 3.51$, $p = .07$; accuracy, $F(1, 36) = 2.14$, $p = .15$). Notably, these patterns were not influenced by agonist medication state for either RT or accuracy (ICB × Agonist × Correspondence: RT, $F(1, 36) = 0.31$, $p = .58$; accuracy, $F(1, 36) = 1.44$, $p = .24$).

We next turn to distributional analyses for the more focused insights they may provide about the expression and suppression of action impulses.

Response Capture by Incorrect Action Impulses

Visual examination of the CAFs in Figure 4A highlights, as we have reported in our previous work, the absence of uniformity in accuracy across the RT distribution. To analyze these patterns, we first included all bins of the CAF in the analysis (bins factor) before focusing on patients' accuracy rates at the fastest RT bin for Cs and Nc trials when they were either on- or off-agonist medication. We report
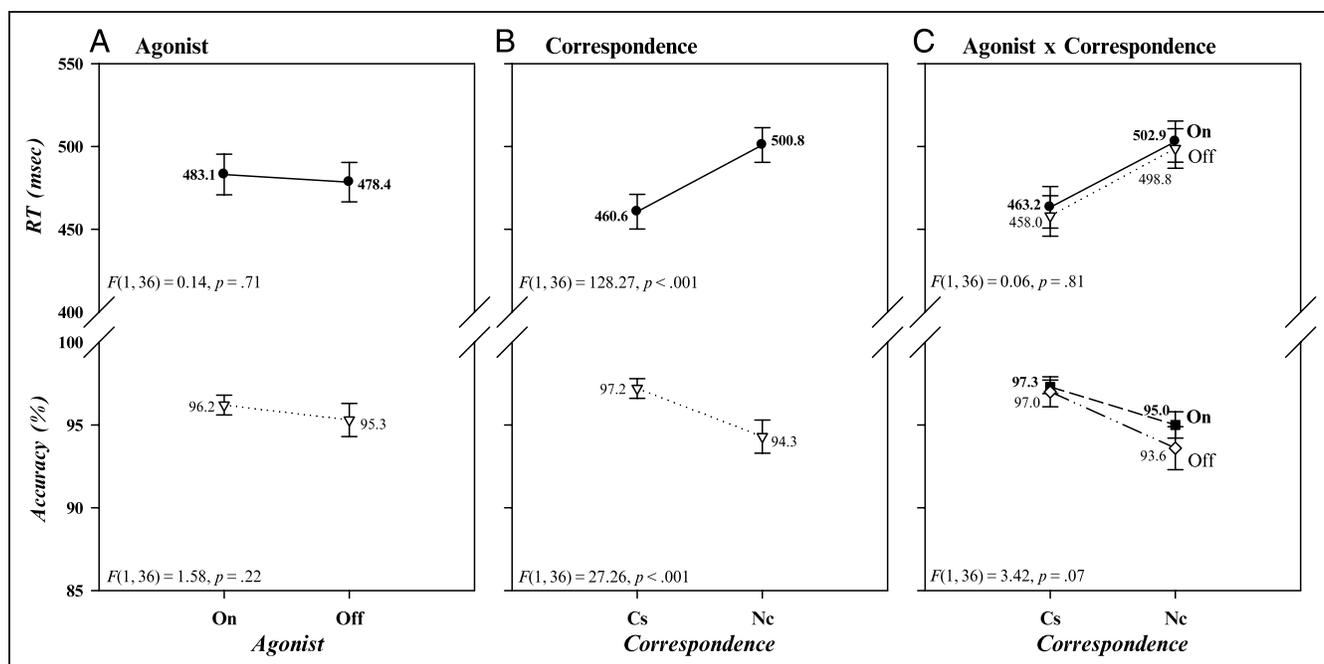

Figure 2. Mean RTs and accuracy rates (% correct) for the entire sample of PD patients as a function of (A) agonist state (on, off), (B) Simon correspondence (Cs, Nc), and (C) the interaction between agonist state and Simon correspondence. Error bars reflect *SEM*s.
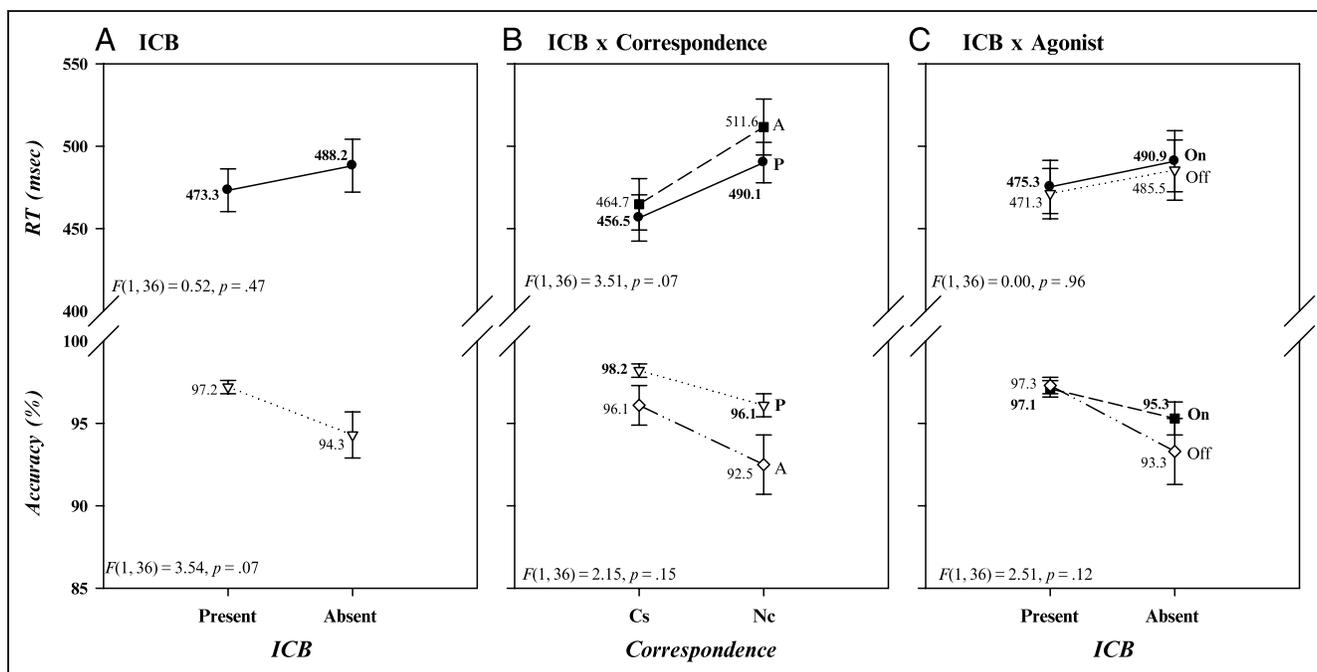
Figure 3. Mean RTs and accuracy rates (% correct) for the entire sample of PD patients as a function of (A) ICBs (present, absent), (B) the interaction between ICB (P = present, A = absent) and Simon correspondence (Cs, Nc), and (C) the interaction between ICB and agonist state (on, off). Error bars reflect *SEM*s.

the interaction terms containing the bins factor as the relationships between the other factors remained consistent with the mean accuracy analyses.

Figure 4A reveals a striking difference in the percentage of errors for Cs and Nc trials across the bins of the RT

distribution (Bins × Correspondence: $F(6, 31) = 10.76, p < .001$). 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
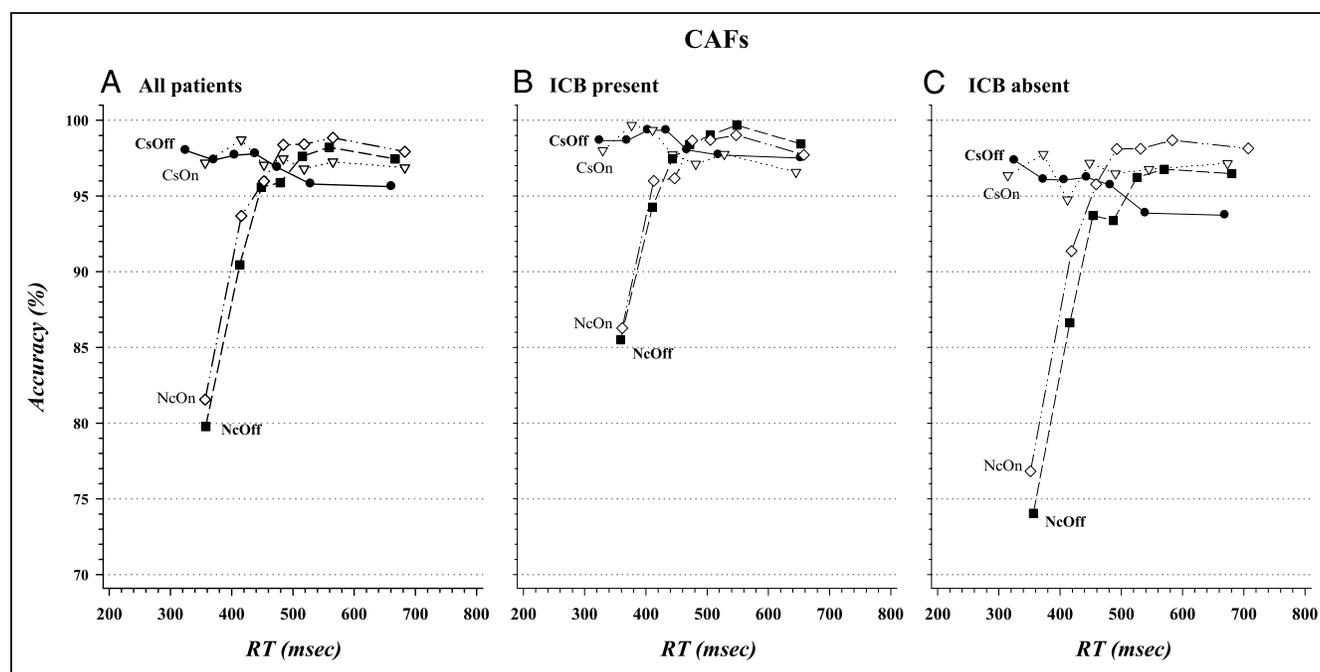

Figure 4. CAFs for Cs and Nc trial types as a function of dopamine agonist state (off vs. on) for (A) all patients, (B) patients with ICBs, and (C) patients without ICB. Across panels, it is clear that errors are associated with the fastest RTs on Nc trials but that the pattern of error rates does not differ between agonist states. B and C indicate that patients with ICB made fewer fast, impulsive action errors than patients without ICB.

low error rates. It is apparent as well that the patterns of errors across bins were not influenced by agonist state (Agonist × Bins: $F(6, 31) = 1.15, p = .36$; Agonist × Bins × ICB: $F(6, 31) = 0.36, p = .90$; Agonist × Bins × Correspondence: $F(6, 31) = 1.01, p = .44$; Agonist × Bins × ICB × Correspondence: $F(6, 31) = 0.97, p = .46$). Even a focused analysis on the fastest bin of accuracy rates confirmed that the higher percentage of fast errors on Nc than on Cs trials (Correspondence: $F(1, 36) = 58.13$, $p < .001$) was unaltered by agonist state (Agonist × Correspondence: $F(1, 36) = 0.69, p = .41$). Within the conceptual framework of the DPAS model, these results support the conclusion that patients experienced early response capture by incorrect action impulses on Nc trials that was not influenced by dopamine agonist medication.

As is apparent in Figure 4B and C, the presence or absence of ICB produced differential patterns of error rates for Nc and Cs trials across the RT distribution (ICB × Bins × Correspondence: $F(6, 31) = 2.86, p < .05$). Guided by the DPAS model, analyzing accuracy rates for the fastest bin of trials showed that the percentage of fast errors was lower among patients with present ICB as opposed to patients without ICB (ICB: $F(1, 36) = 4.40, p < .05$). Importantly, this effect varied with the correspondence of the stimulus–response mapping (ICB × Correspondence: $F(1, 36) = 5.03, p < .05$). Specifically, both patient groups had comparably low fast error rates on Cs trials (~2–3%), whereas patients without ICB had a much higher percentage of fast errors on Nc trials than did patients with ICB (25 vs. 14%; $F(1, 36) = 4.93, p < .05$). This suggests that patients with ICB experienced less initial response system capture by the activation of incorrect action impulses than did patients who were not manifesting ICB symptoms. Notably, these differences in fast errors were unaffected by agonist state (ICB × Agonist: $F(1, 36) = .05, p = .83$), irrespective of stimulus–response correspondence (ICB × Agonist × Correspondence: $F(1, 36) = .13, p = .72$).

Suppressing Interfering Action Impulses

Consistent with our previous work, the delta plots in Figure 5A reveal variations in the size of the Simon effect across the RT distribution. 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 slope of the segment connecting the final two delta values of the delta plot provides the most sensitive metric of the proficiency of inhibitory control. We first included slopes from all segments of the delta plot in the analysis (segment factor) before focusing on a comparison of the slopes from the final delta segment.

As can be seen in Figure 5A, early in processing the slopes of the delta plot were positive, indicating an initial increase in interference, whereas later in processing the slopes were negative, reflecting suppression of that early interference (segment: $F(5, 32) = 14.20, p < .001$). This overall form of the delta plot was not influenced by agonist
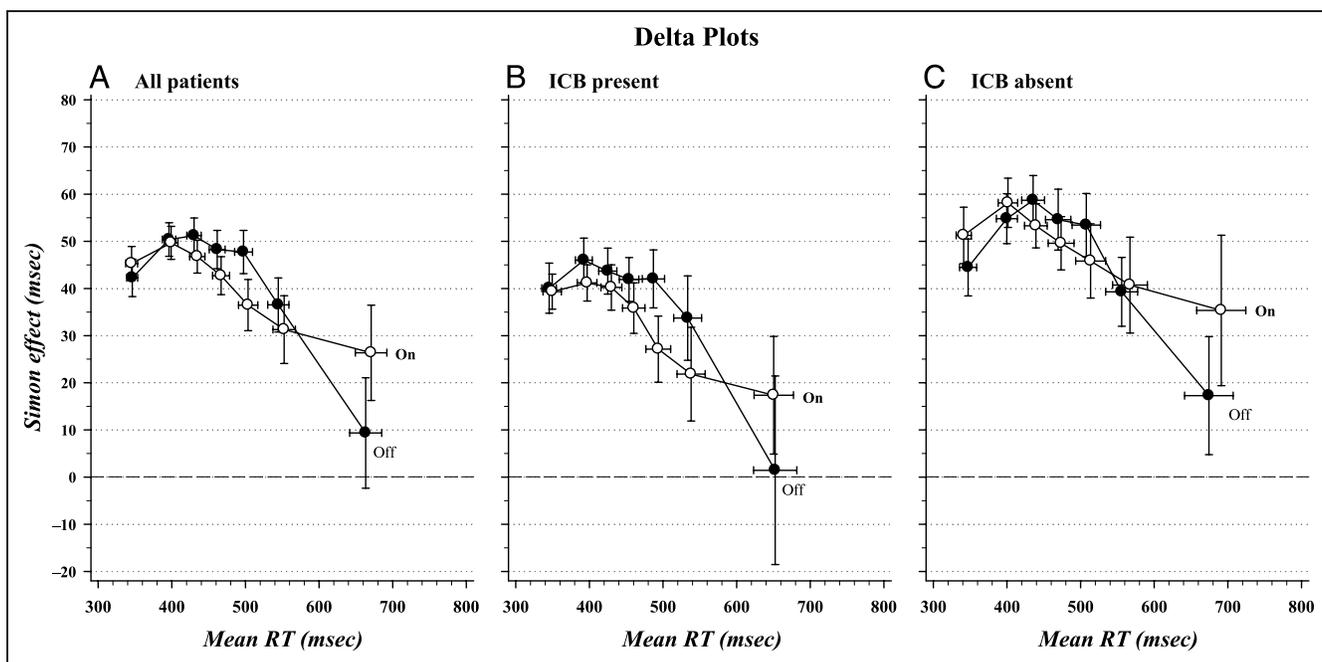

Figure 5. RT delta plots as a function of agonist state for (A) all patients, (B) patients with ICBs, and (C) patients without ICB. Across panels, delta slopes diverge at the slow end of the distribution, indicating more proficient suppression (steeper negative-going delta slope) of action impulses in the off-agonist state and less proficient suppression under the acute influence of dopamine agonist medication. Suppression slopes were uninfluenced by the presence or absence of ICB.

medication state (agonist: $F(1, 36) = 0.02, p = .89$). However, agonist medication state did produce differential effects on the slopes of the segments across the RT distribution (Agonist × Segment: $F(5, 32) = 3.09, p = .007$). It is evident in Figure 5A that the slope of the final segment of the delta plot, which is most sensitive to inhibitory proficiency, is less negative-going when patients were on their agonists ($m = -0.05, SEM = .05$) as opposed to when they were off their agonists ($m = -0.23, SEM = .06; F(1, 36) = 4.40, p < .05$). According to the DPAS model, this suggests that patients were less effective at suppressing interference when they were under the influence of their agonist medications.

The delta plots derived separately for patients with and without ICB are shown in Figure 5B and 5C. The presence or absence of these symptoms did not influence the forms of the delta plots when all slopes were included in the analysis (all $ps > .25$). Moreover, final delta slope values were similar between patients with ICB ($m = .15$) and patients without ICB ($m = .13$; ICB: $F(1, 36) = 0.08, p = .78$), and this pattern was not affected differentially by agonist state (ICB × Agonist: $F(1, 36) = 0.31, p = .58$). This pattern of effects confirms that the temporal dynamics of response suppression did not vary with the presence or absence of ICB.

Association of Agonist Dosage to the Expression and Suppression of Action Impulses

Correlational analyses focused on the association between daily agonist dose (expressed in milligrams of LEDD) and both the strength of response capture by action impulses (i.e., fast errors) and the proficiency of suppression (i.e., final delta slope) during the on-agonist state. Agonist dosage was unrelated to the strength of response capture ($r = .11, p = .52$) but was positively associated with the final slope value ($r = .37, p = .02$; Figure 6). The latter is consistent with the interpretation that higher daily doses of dopamine agonist are associated with more positive delta slope values and, by inference, less proficient suppression of action impulses.

Dependence of Agonist Effects on Baseline Performance

We tested whether agonist effects are dependent on baseline performance in the off-agonist state. We predicted that individuals with low baseline proficiency of suppression in the off-agonist state would show improved suppression under the influence of dopamine agonist medication, whereas individuals with high baseline proficiency of suppression in the off state would show a reduction in suppression in the on-agonist state. This prediction was supported across the entire sample by a pronounced negative correlation between change and initial value ($r = -.82, p < .001$), indicating that high and low
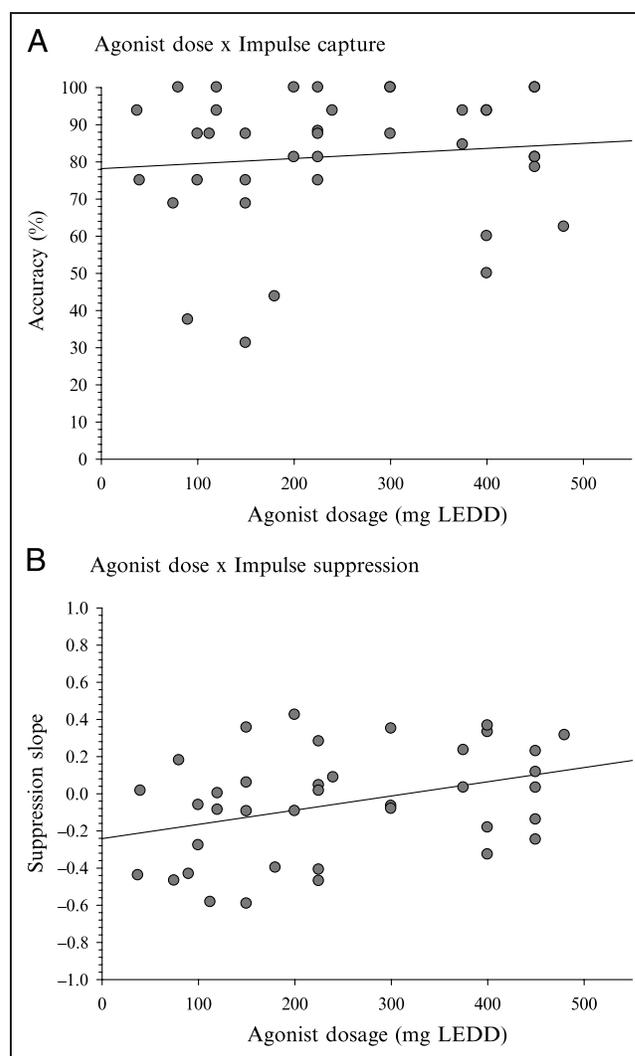

Figure 6. Scatterplots depicting (A) the absence of an association between agonist dosage and fast, impulsive errors and (B) the significant positive association ($r = .37$) between agonist dosage and the suppression slope from the final segment of the delta plot. In B, more positive slope values reflect less-proficient inhibitory control. Agonist dosage is expressed in milligrams of LEDD.

suppression values in the off-agonist state were associated with reversed patterns in the on-agonist state.

Ruling out Alternative Explanations

It is tempting to interpret the strong correlation between initial value and change as an indication that effects of agonist medication depend on individual baseline performances. However, an alternative explanation for this correlation is that it is due to regression to the mean. That is, a correlation of $-.68$ is already expected even in the absence of a genuine relationship between initial value and change (cf. Tu & Gilthorpe, 2007, p. 446). To rule out regression to the mean, we applied a conservative testing procedure that yields a more reliable test of the genuine relationship between initial value and change (Tu &

Gilthorpe, 2007; Geenen & van de Vijver, 1993). If, in fact, poor suppressors benefit and good suppressors worsen on-agonist medication, it follows that the variance of the suppression measure should be significantly lower in the on than in the off medication state (cf. Myrtek & Foerster, 1986).[2] The test of the equality of variances between the two conditions (Tu & Gilthorpe, 2007, Equation 4) revealed that the variance of the suppression measure in the on medication state (variance = .09) was significantly lower than in the off state (variance = .16; $t(36) = 1.68$, $p = .05$), thus strengthening our confidence in the predicted relationship between change and initial value. This set of additional analyses shows that the observed agonist effects on suppression are driven by individual baseline differences and cannot be explained solely in terms of regression to the mean.

It is also possible that baseline differences in suppression in the off-agonist state can be accounted for by individual differences in clinical or general performance factors. However, the proficiency of suppression in the off-agonist state did not correlate with motor symptom severity, age, disease duration, agonist and total LEDD, time on agonist, mean RT, or fast errors (all $ps > .15$).

DISCUSSION

The activation of incorrect motor impulses in the Simon task produced clear interference on Nc trials as evidenced by a slowing of mean RT and a reduction in mean accuracy rates compared with Cs trials. More importantly, the distributional analyses revealed patterns of effects that were not evident in the mean results and conformed to the predictions of the DPAS model. First, the CAFs were characterized by a pattern of predominantly fast errors on Nc trials that is consistent with rapid response system capture by incorrect action impulses, which breech the threshold for response execution and escape inhibitory control. Second, on conflict trials in which incorrect activation did not produce an overt response error (i.e., a correct response was made), the delta plots nonetheless exposed RT interference that increased across the faster segments and then reversed dramatically at the slow end of the RT distribution. This steep reduction is consistent with a late effect of top–down inhibitory control that takes time to buildup within a trial and is most effective on slower reactions. These patterns, which replicate previous studies, provided the opportunity to directly test the effects of dopamine agonist state and susceptibility to ICBs on both the expression and suppression of action impulses in PD patients.

Dopamine Agonists Can Impair Suppression of Action Impulses

The current data reveal differential effects of dopamine agonist medication on response capture by action impulses and inhibitory control engaged to suppress interference produced by this capture. As revealed by the CAFs, susceptibility to making fast, impulsive errors on Nc trials did not vary with agonist state. This argues against the interpretation that dopamine agonists alter the motor system by making it more susceptible to capture by stimulus-driven action impulses. In contrast, dopamine agonists disrupted cognitive control processes that are engaged reactively to suppress motor system interference by the activation of impulsive actions. Specifically, patients under the acute influence of their agonists were less proficient at suppressing interference (i.e., display a less negative-going delta slope toward the slow end of the RT distribution) compared with when they were temporarily withdrawn from agonist medication. Additionally, higher doses of agonist tended to correlate with less-proficient suppression ability. Taken together, these findings suggest that agonists do not predispose speeded decision-making to stronger capture by stimulus-driven response impulses but instead impair the ability to inhibit these actions from interfering with goal-directed behavior. Previous studies show that PD impairs inhibitory action control (Wylie, Ridderinkhof, Bashore, et al., 2010; Praamstra et al., 1998), but the current study demonstrates that a medication intended to ameliorate clinical motor symptoms can further disrupt this key component of the brain's cognitive control system.

PD Agonist Effects on Inhibitory Action Control Depend on Baseline Performance

The effects of agonist medication on inhibitory control were sensitive to baseline performance when the patient was withdrawn from agonist medication. Specifically, patients who were most proficient at suppressing action impulses in the off-agonist state experienced a significant reduction in inhibitory control when they were under the influence of the agonist. In contrast, patients who were relatively poor at suppressing action impulses when off of their agonists showed improved inhibitory control under the influence of an agonist. Analyses indicated that these effects could not be accounted for solely by regression to the mean. These paradoxical effects of agonist medication on cognitive control resemble patterns observed in other studies of dopamine effects on cognition that suggest that an inverted U-shaped curve accounts for some relationships between cognitive performance and dopamine function (Cools & D'Esposito, 2011). This account rests on the assumption that peak performance on cognitive measures sensitive to dopamine function depends on optimal dopamine levels but that reductions (e.g., due to pathology) or overdoses (e.g., due to medications) of dopamine lead to suboptimal cognitive performance (Cools, Barker, Sahakian, & Robbins, 2001a; Swainson et al., 2000; Gotham, Brown, & Marsden, 1988). On the basis of this account, patients with dopamine pathology that affects inhibitory control circuits of the BG would be expected to show poor inhibitory control in the off-agonist state that could be partially restored when dopamine levels are

increased by agonist medication. In contrast, proficient inhibitory control in the off-agonist state suggests a relative sparing of dopamine pathology in inhibitory control circuits of the BG. With the addition of agonist medication, the enhanced dopamine levels would then "overdose" these circuits and impair inhibitory control performance. Similar patterns of effects in PD have been demonstrated in studies of working memory and reversal learning (Cools & D'Esposito, 2011; Costa et al., 2003; Cools et al., 2001a; Cools, Barker, Sahakian, & Robbins, 2001b).

Patients with ICBs Are Not More Susceptible to Motor Impulses

A complementary aim of the study was to determine if the emergence of ICB involves a specific deficit in impulse control over prepotent action impulses. Our results indicate that patients displaying ICB did not experience either stronger activation of action impulses or a greater reduction in inhibitory control under the influence of a dopamine agonist relative to patients without ICB. These patterns argue against the notion that the emergence of ICB involves increased susceptibility to impulsive motor behavior (see also Djamshidian, O'Sullivan, Lees, & Averbeck, 2011). Quite to the contrary, patients with ICB showed a trend toward reduced interference and committed fewer fast errors on Nc trials compared with patients without ICB, suggesting that these patients were actually less susceptible to impulse capture by the processing of irrelevant stimulus information. In fact, despite similar RTs, the ICB patients in this study committed fewer fast, impulsive action errors than healthy controls without PD, whose data were reported in two previous studies that used a similar experimental task and design (Wylie, Ridderinkhof, Bashore, et al., 2010; Wylie, Ridderinkhof, Elias, et al., 2010). Given that the DPAS model asserts that early response capture reflects the strength of bottom–up activation of a conflicting response, this might suggest that ICB patients either are more effective at fast action selection under conflict or experience less buildup of stimulus-driven response activation. Although this finding requires additional investigation, it seems to suggest that control over impulsive manual actions as revealed by the Simon task may not be sensitive to the impulsive behaviors displayed by patients with ICB.

Other forms of impulsivity outside the motor domain may be more important to understanding the mechanisms underlying ICB in PD, such as an inclination toward taking higher risks, difficulties restraining pursuit of immediate rewards and delaying action to obtain higher rewards, pursuing immediate pleasures with little forethought about potential negative consequences, or issuing decisions before all relevant information is obtained (Evenden, 1999). In fact, "impulsive action" and "impulsive decision-making" are argued to involve distinct time courses, mediate influences (e.g., reward, risk), and underlie neural mechanisms (Eagle & Baunez, 2010). The emergence of ICB in PD appears to be driven largely by impulsive decision-making

as ICB patients show a greater propensity for anticipating and learning from rewarding experiences, preferring smaller immediate rewards over larger delayed rewards, and taking greater risks to obtain reward under the influence of agonists (Claassen et al., 2011; Milenkova et al., 2011; Voon et al., 2010, 2011; Housden et al., 2010). Imaging studies of patients with ICB also point to distinguishing features in mesolimbic function, which is implicated in reward, risk, and outcome-based learning and decision-making (O'Sullivan et al., 2011; Rao et al., 2010; van Eimeren et al., 2010; Steeves et al., 2009; Thiel et al., 2003). Thus, the absence of an ICB influence on inhibitory action control may be because of the fact that the specific vulnerability in this group of patients is linked closely to abnormal mesolimbic activity.

Potential Agonist Effects on the Neural Mechanisms of Inhibitory Control

Animal studies indicate that dopamine's influence on inhibitory control over motor behavior involves its modulating influence in dorsal (via nigrostriatal pathways) as opposed to ventral (via mesocorticolimbic pathways) striatal regions (Eagle et al., 2011; Eagle & Robbins, 2003). The posterior regions of the dorsal striatum (e.g., the putamen), which are tightly linked to basic motor processes, are affected earliest by the dopamine pathology in PD (McAuley, 2003; Kaasinen & Rinne, 2002). Cognitive control functions, including inhibitory action control, are linked to relatively anterior regions of the dorsal striatum (e.g., caudate nucleus), which can be impacted quite variably across early to moderate stages of PD (Lewis, Dove, Robbins, Barker, & Owen, 2003; Kaasinen & Rinne, 2002). Across individuals, differential degrees of dopamine depletion in this region may explain the paradoxical response to agonist medication described above (Rowe et al., 2008). Alternatively, the detrimental effect of agonist medication on inhibitory control may reflect its differential impact on D1-mediated pathways (i.e., direct or go routes), which give rise to action selection, and D2-mediated pathways (indirect or no-go routes), which are involved in the selective suppression of actions (Claffey, Sheldon, Stinear, Verbruggen, & Aron, 2010; Aron & Verbruggen, 2008; Aron, 2007). Dopamine agonists have a higher affinity for D2-like receptors, potentially driving the bias of activity toward the inhibition of the indirect or no-go pathways (Dodd et al., 2005; Frank, 2005; Black et al., 2002). Because the activation of D2 receptors putatively inhibits the indirect pathway, the net effect would be a reduction in selective suppression.

At a broader network level, studies of neural activation patterns associated with response interference trials on conflict tasks (e.g., Simon and Flanker tasks) highlight the involvement of fronto-parietal and fronto-striatal networks (e.g., Schumacher, Cole, & D'Esposito, 2007; Hazeltine, Diedrichsen, Kennerley, & Ivry, 2003; Peterson et al., 2002; Casey et al., 2000; Pardo, Pardo, Janer, & Raichle, 1990; for a meta-analysis, see Nee, Wager, & Jonides, 2007; for a review, see Ridderinkhof, van den Wildenberg, & Wylie, 2011).

Conflict trials afford two competing actions, one prepotent and the other goal-directed. These action affordances are likely instantiated by circuits connecting posterior parietal to premotor cortices, which are thought to form the basis of association-driven visuomotor transformations (Ridderinkhof, Forstmann, et al., 2011; Sturmer, Redlich, Irlbacher, & Brandt, 2007). The resolution of this conflict may come from different sources, including lateral inhibition within motor areas or by an enhancement of activation in brain areas involved in directing action selection, such as the pre-SMA (Cisek, 2007; Ullsperger & von Cramon, 2001). In fact, individual differences in the susceptibility to capture by the prepotent response in the Simon task are accompanied by stronger activation in the pre-SMA, which is consistent with a heightened demand on action selection (Forstmann, Jahfari, et al., 2008).

The resolution of conflict in the Simon task also depends critically on the engagement of neural circuitry involved in top–down inhibitory action control (van den Wildenberg et al., 2010; Burle, Vidal, Tandonnet, & Hasbroucq, 2004). For example, healthy adults who are more proficient at suppressing impulsive actions in the Simon task (i.e., have a steeper negative-going final delta slope) show greater activation of the right inferior frontal cortex (rIFC; Forstmann, Jahfari, et al., 2008). Interestingly, activation patterns in the pre-SMA that were linked to fast response capture were unrelated to variations in the proficiency of suppression. Other imaging studies have also highlighted involvement of rIFC in selective inhibitory control in situations of action conflict (Jahfari et al., 2011; Davelaar, 2008; Forstmann, van den Wildenberg, et al., 2008). These findings are consistent with existing models describing a central role for rIFC and its efferent projections to the BG in inhibitory action control (see Aron et al., 2007). The current findings also suggest the possibility that these putative inhibitory control circuits may be modulated directly by dopamine agonist medication in PD patients.

Study Limitations and Extant Issues

There are a few limitations and extant issues worth addressing. We measured the acute influence of dopamine agonists; thus, the chronic effects of agonists on impulse and inhibitory control remain unknown. Although an 18- to 24-hr withdrawal period was sufficient to reveal agonist effects in the current study, it remains an open question as to how washout periods of different durations impact cognitive performance in PD. We did not manipulate levodopa administration, and the majority of patients was taking levodopa and remained under the influence of this dopamine medication during both testing sessions. Thus, dopaminergic activity was still impacted by levodopa even when patients were withdrawn from their agonists. Notably, the between-subject factor accounting for levodopa status did not influence the dynamics of response capture or suppression of action impulses (see Supplementary Material). In animal work, levodopa

has been shown to alter the expression of impulsive behavior (Pattij & Vanderschuren, 2008). Neuropsychological studies comparing levodopa and agonist effects have produced mixed results (Brusa et al., 2003). Future studies of cognitive control in PD would clearly benefit from within-subject designs that test patient performance under the selective influence of dopamine-modifying medications. The ICB group included patients presenting with various forms of ICBs, which could introduce an important source of variability in impulsive motor control. The mechanisms underlying the variable expressions of ICB and the contextual factors that play a role in the development of ICB remain poorly understood. We considered potential differences between two broad subgroups of ICB patients, specifically patients presenting with primary problems controlling gambling and buying behaviors ($n = 10$) versus patients presenting primarily with compulsive sexuality, eating, and/or hobbyism ($n = 9$), but these subgroups showed no significant differences in performance. In fact, both groups showed a similar reduction in fast, impulsive errors compared with patients without ICB in this study and healthy controls from previous work.

In a previous study, we showed that deep brain stimulation (DBS) of the subthalamic nucleus (STN) in PD patients with moderate motor symptoms improved the proficiency of inhibitory control over action impulses in the Simon task (Wylie, Ridderinkhof, Elias, et al., 2010) and prepotent responses (van den Wildenberg et al., 2006). How can we reconcile the apparent discrepancies between the effects of agonist medication and of STN DBS on suppression? It is important to point out that patients in the STN DBS study showed poor suppression when stimulation was not being delivered; in fact, the performance of this group of patients was similar to the patients in the current study who were poor suppressors when they were not taking their agonist medications. Thus, both of these groups of poor suppressors benefitted from their respective treatment. This suggests that these treatments may result in a common final effect, but this improvement in suppression is best realized among patients who are poor at suppressing when their treatment is withdrawn and likely suffering from advanced dopamine depletion in cognitive control circuits of the BG (Wylie, Ridderinkhof, Bashore, et al., 2010).

Conclusions

Individuals with PD are generally less proficient at suppressing involuntarily activated action impulses. This study offers empirical demonstration that dopamine agonists alter the proficiency of inhibiting action impulses, and these effects depend on baseline performance. The presence of ICB did not exacerbate impulsive response errors or difficulties inhibiting interfering response impulses; in fact, ICB patients showed reduced susceptibility to acting on motor impulses. The development of tools to measure motor and cognitive functions that are sensitive to dopamine medication is essential to formulating treatment

decisions that optimize basic motor and cognitive control processes in PD patients. This is particularly true of dopamine agonist medication, which can impact motor, cognitive, affective, and reward processing functions as well as predispose to rather dramatic and disruptive behavioral changes.

Notes

1. The DPAS model is agnostic about what happens precisely at intermediate bins of the RT distribution apart from the general expectation that increasing interference effects across early and middle latencies of the RT distribution will turn into a negative-going slope at the slow end of the distribution. The DPAS model specifies that the dynamic change in the magnitude of the interference effect as a function of time is best captured by the slope of the delta plot for slow RTs (i.e., the final delta slope). For a detailed review of empirical evidence supporting this conjecture, see van den Wildenberg et al. (2010).

2. Because this analysis method is sensitive to differences in measurement error between conditions, we first tested the underlying assumption that the measurement error was equally distributed across medication state conditions. For each participant, we computed the standard deviation of RT for each level of bin, correspondence, and agonist and submitted these values to a repeated-measures ANOVA. This analysis verified that dopamine agonist administration did not systematically affect RT variability ($F < 1$, for main effect of agonist and all interactions with agonist).

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