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Overriding Actions in Parkinson's Disease: Impaired Stopping and Changing of Motor Responses

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We administered a stop-change paradigm, an extended version of the stop task that requires (a) stopping an ongoing motor response and (b) changing to an alternative (change) response. Performance of a group of patients diagnosed with Parkinson's disease (PD) and taking dopaminergic medication was compared with that of matched healthy control (HC) participants. Behavioral results indicated that response latencies to the initial go signal did not distinguish between the 2 groups, but that stopping latencies were prolonged in PD patients. In addition, the change response was delayed in the clinical group, indicating difficulties in flexibly changing to alternative motor actions upon external cues. The change deficit in PD related to the inhibition deficit. This dependence points to a serial processing architecture in PD according to which the stopping process has to finish before the change process can be initiated. In contrast, the HC group showed parallel stop and change processing. Analyses of sequential trial effects suggest that both HC and PD patients are susceptible to aftereffects of action override, due to the consequences of the automatic retrieval of recent associations between action and goal representations. Interestingly, postchange performance of the clinical group was hampered disproportionately, suggesting that PD is associated with an impairment in overriding previously formed action-goal associations. These findings support the notion that both higher-order cognitive control processes, such as inhibiting and changing actions, as well as lower-order feature binding mechanisms rely on basal ganglia functioning and are compromised by the basal ganglia dysfunction caused by PD.

Keywords: Parkinson's disease, inhibitory motor control, stop-change task, SSRT, aftereffects of action override

The ability to inhibit ongoing motor actions constitutes a hallmark of cognitive control over behavior (Logan, 1994). Stopping an action when it is no longer appropriate is a first and necessary step toward flexible behavioral adjustments to pertinent changes in the environment. For example, one can very quickly abort typing a message on a computer's keyboard upon hearing a "new e-mail alert" and reach for the mouse to open the e-mail inbox. Frontal-basal ganglia circuitry has been identified as a vital network for the selection and inhibition of voluntary actions (for a review, see Ridderinkhof et al., 2011). Accordingly, numerous neurological disorders related to frontal-basal ganglia dysfunction (such as Huntington's disease, Tourette's syndrome, Parkinson's disease) and neuropsychiatric conditions (e.g., schizophrenia, attention deficit hyperactivity disorder, obsessive–compulsive disorder) have been associated with various forms of suboptimal inhibitory action control (Gauggel, Rieger, & Feghoff, 2004; Nigg, 2005; Penadés et al., 2007; Wylie, Ridderinkhof, Bashore, & van den Wildenberg, 2010). This study extends previous work on inhibitory motor control in Parkinson's disease (PD) by focusing on two vital aspects of action control that are illustrated by the computer example above. These are (a) the proficiency in stopping ongoing voluntary movements upon the appearance of an external stop signal and (b) the proficiency in changing actions, that is, flexibly

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changing behavior by executing an alternative motor action. First, we provide an overview of relevant clinical studies on the relation between PD and inhibitory control over integrative sensorimotor actions and then we introduce the theoretical cognitive framework for investigating stopping and changing provided, respectively, by the stop-signal and stop-change paradigms.

Inhibitory Action Control in Parkinson's Disease

A key feature of PD involves neurodegeneration of neurons that produce dopamine within the substantia nigra pars compacta of the basal ganglia, which contributes to cardinal clinical motor symptoms of bradykinesia, rigidity, and tremor (Bjorklund & Dunnett, 2007; McAuley, 2003). Apart from affording elementary motor functions, the basal ganglia, via elaborate connections with prefrontal and motor areas of frontal cortex, are hypothesized to play a key role in the distributed neural network that is involved in the focused selection and inhibition of motor actions (Alexander, DeLong, & Strick, 1986; Aron, 2007; Hikosaka, 1998; Mink, 1996; Mink & Thach, 1993; Redgrave, Prescott, & Gurney, 1999; Robbins & Brown, 1990). Upstream basal ganglia projections selectively inhibit the output structures of the basal ganglia that correspond to a particular movement ensemble in order to release thalamo-cortical motor pathways from tonic inhibition (Alexander & Crutcher, 1990; Kropotov & Etlinger, 1999). The *direct pathway* of the basal ganglia includes monosynaptic inhibitory (i.e., GABAergic) projections from input structures (e.g., neostriatum) to output nuclei (e.g., globus pallidus interna, substantia nigra pars reticulata), thereby inhibiting the output structures and, in turn, effectively *dis*inhibiting the thalamus and (pre)motor cortex. Accordingly, the direct pathway is hypothesized to convey a go signal, facilitating the release (and hence, the selection) of motor commands from tonic inhibition (Frank, 2005). A complementary *indirect pathway* exerts an opposite effect by exciting basal ganglia output structures through projections from input structures to various intermediate basal ganglia nuclei (e.g., globus pallidus externa, subthalamic nucleus) that increase inhibition over thalamo-cortical pathways. In addition, a *hyper-direct pathway* that involves direct projections from prefrontal cortex to the subthalamic nucleus of the basal ganglia (a key structure along the indirect pathway) has been linked to experimental situations that call for quick suppression of ongoing action commands (Aron et al., 2007; Aron & Poldrack, 2006; Casey et al., 2000; Jahfari et al., 2011; Nambu, Tokuno, & Takada, 2002). Thus, the basal ganglia constitute a key circuit within the action control network through innervation of the direct, indirect, and hyperdirect pathways that selectively facilitate and suppress action commands (cf., Mink, 1996).

The basal-ganglia model described above provides a theoretical framework for interpreting impairments in inhibitory action control associated with basal-ganglia dysfunction in PD. The importance of understanding the effect of PD on inhibitory action control is underscored by two lines of research. First, clinical studies using conflict tasks show PD-related impairments in suppressing motor impulses that are activated involuntarily (Praamstra, Plat, Meyer, & Horstink, 1999; Wylie et al., 2009; Wylie, Ridderinkhof, Bashore, et al., 2010). Conflict paradigms such as the Eriksen flanker task (Eriksen & Eriksen, 1974) and the exemplary Simon task (Simon, 1969, 1990) provide powerful experimental tools for investigating individual proficiency to resolve response interference when selecting between two competing response alternatives. Conflict trials present stimuli with a task-relevant dimension and a task-irrelevant dimension that are each associated with response alternatives that are mutually exclusive (Kornblum Hasbroucq, & Osman, 1990; Ridderinkhof, 2002). Altered basal ganglia function due to dopamine depletion in PD reduces the proficiency of resolving response conflict (Praamstra, Stegeman, Cools, & Horstink, 1998). Although PD patients and HC often display similar mean interference effects on reaction time (RT), distributional analyses reveal that PD patients were less proficient in selectively suppressing incorrect response activation in order to resolve the interference (van Wouwe et al., 2017; Wylie, Ridderinkhof, Bashore, et al., 2010). In addition, patients' ability to overcome interference by conflicting response tendencies declined with disease severity as indexed by a motor symptom rating scale (Wylie, Ridderinkhof, Bashore, et al., 2010).

The effects of clinical interventions that ameliorate the motor symptoms of PD on interference control underscore the pivotal role of the basal ganglia. The intake of dopamine agonists affects interference resolution. More specifically, proficient suppressors tested off agonist medication showed less efficient suppression when on agonists, whereas less-proficient suppressors tested off agonists showed improved suppression on agonists (Cools & D'Esposito, 2011; Wylie, Claassen et al., 2012). Another therapeutic intervention, namely deep-brain stimulation (DBS) of the subthalamic nucleus (STN), results in two dissociable effects. First, stimulation increased impulsive, premature responding in conflict situations, indicated by a high incidence of fast response errors. Second however, on correct trials with relatively long response latencies, STN stimulation was associated with improved proficiency of impulse suppression, thereby facilitating the selection of the correct action (Wylie, Ridderinkhof, Elias, et al., 2010).

A second line of empirical evidence linking basal ganglia dysfunction in PD to deficits in inhibitory control is bolstered by a handful of stop-signal task studies. The classical stop-signal task provides a paradigmatic case of response inhibition that has deepened our understanding of inhibitory processes since the pioneering work of Logan (1982; Logan & Cowan, 1984; see Verbruggen & Logan, 2008a for a review, for earlier examples, see Lappin & Eriksen, 1966 and Vince, 1948). In a typical variant of this task, participants are instructed to make discriminative manual responses to one of two visual stimuli, the *go stimulus*, while being prepared to inhibit either response upon the occasional appearance of another stimulus (i.e., the *stop signal*) that can occur shortly after the onset of the go stimulus. As an example, participants may be instructed to make a left button press when a leftward-pointing arrow appears and a right button press when a rightward-pointing arrow appears, but to inhibit the signaled response whenever an auditory tone is presented shortly after the arrow's appearance. Performance on stop-signal trials has been conceptualized as a race between two independent processes, the go and stop processes that are triggered, respectively, by the onsets of the go stimulus and the stop signal (Boucher, Palmeri, Logan, & Schall, 2007; Logan & Cowan, 1984). If the go process wins the race, inhibition fails. However, if the stop process wins the race, the motor response is inhibited successfully. A major advantage of the stop task over other experimental tasks that tap into inhibitory control, such as go/no-go tasks and Stroop tasks as well as more complex neuro-

psychological tests like the Wisconsin Card Sorting Test, is that the latency of the covert response inhibition process, the *stop-signal RT* (SSRT), can be estimated within the conceptual framework of the race model (see Figure 1; see Method section for elaboration).

Comparing patients and HC groups, Gauggel, Rieger, and Feghoff (2004) demonstrated that PD experience slower stopping control over ongoing actions, despite comparable response latencies to go signals. A specific involvement of the STN in inhibitory action control was supported by the finding that deep-brain stimulation of the STN, which ameliorates the motor symptoms of PD, also improved the patients' ability to inhibit their actions upon presentation of a stop signal as indicated by shorter SSRT when DBS was on compared with a (within-subject) condition without DBS (Mirabella et al., 2012; Swann et al., 2011; van den Wildenberg et al., 2006; but see Obeso, Wilkinson, Rodriguez-Oroz, Obeso, & Jahanshahi, 2013; Ray et al., 2009).

Changing Actions: The Stop-Change Paradigm

In everyday life, stopping of unwanted actions is often followed by the production of an alternative action that meets the changed action goal. Thus, the abortion of responses in an all-or-none manner, like that required in the stop task, seldom takes place in isolation. To assess the processes engaged in stopping one action and initiating another, we used an extended version of the stop task, called the *stop-change task*, introduced by Logan and colleagues (Logan, 1982; Logan & Burkell, 1986). Several variants of the stop-change task have been developed since its introduction. Most of these include two task components (i.e., the GO1 and the GO2 task), each associated with different response output goals. The GO2 task might involve, for example, quickly pressing a third button that was not part of the GO1 response configuration (Boecker, Buecheler, Schroeter, & Gauggel, 2007; de Jong, Coles, & Logan, 1995; Logan & Burkell, 1986; Schachar, Tannock, Marriott, & Logan, 1995; Verbruggen & Logan, 2008b). Alternatively, the GO2 task might involve reversing the GO1 response (e.g., Brown & Braver, 2005; Krämer, Knight, & Münte, 2011; Nachev, Wydell, O'Neill, Husain, & Kennard, 2007). To succeed on the stop-change task, participants must (i) respond efficiently to the go stimulus when a stop-change signal does not occur, as required on a majority of trials (e.g. ⬅, left button press); while (b) being prepared to inhibit their initial response activation to the go stimulus when the stop-change signal occurs; and (c) to activate the alternative response (e.g., right button press). Thus, there is a tripartite performance goal structure when changing a response: efficient production of responses to go stimuli (GO1), proficient inhibition of those responses when required (STOP), and efficient production of alternative responses (GO2). Formal tests of various alternative models have indicated that the behavioral data are explained best in terms of both a nondeterministic serial activation of cognitive processes (i.e., GO1 is replaced by STOP, is replaced by GO2) as well as by a limited-capacity parallel activation of these processes (STOP and GO2 occur simultaneously) that operates similarly to the serial processing architecture (Verbruggen, Schneider, & Logan, 2008). Importantly, activating the alternative GO2 response requires inhibition of the GO1 response (Verbruggen & Logan, 2008c). Inhibition latencies in the stop-change task are generally prolonged compared with inhibition latencies in the standard stop task (Bekker et al., 2005; Boecker et al., 2007, 2011; de Jong et al., 1995; Logan & Burkell, 1986).

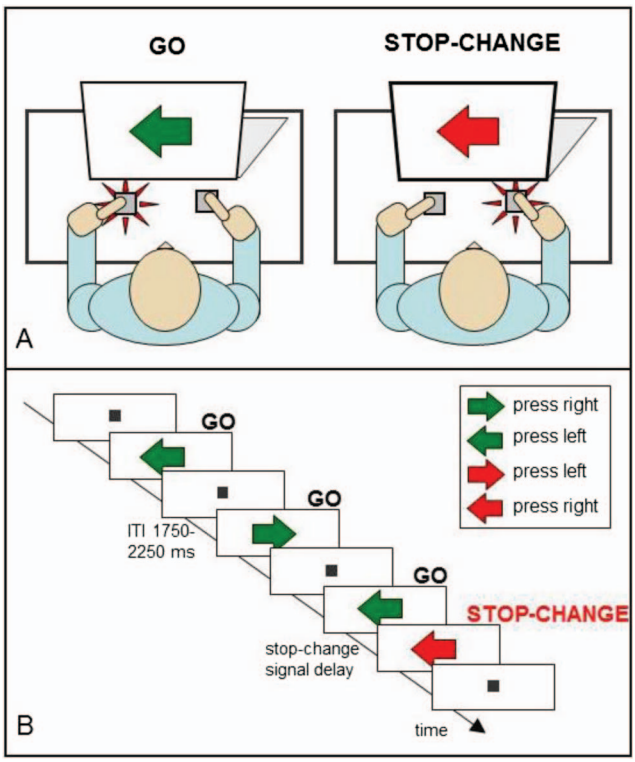

Figure 1. Stop-change task. Participants were instructed to press the left or right button in the direction indicated by the green arrow (i.e., go trials). On 30% of the trials, the color of the arrow changed from green to red (i.e., stop-change trials) upon which participants should inhibit the go response and execute the alternative response. Upon presentation of the stop-change signal in this example, participants should inhibit the left-hand response and execute the right-hand response instead. See the online article for the color version of this figure.

The Present Study

To date, the *stop-change* paradigm has never been applied to study the ability to override actions in patients diagnosed with PD. Administering the stop-change task provides the opportunity to enhance our insight into the nature of action control dysfunction associated with PD, and more specifically on the ability to flexibly stop and change motor responses. A group of HC and a group of medicated patients diagnosed with PD issued symbolically compatible left- or right-button presses in response to a leftward- or rightward pointing green arrow ("*To green arrows pointing left, press the left response button with your left hand;*" "*To green arrows pointing right, press the right button with your right hand*"). This constituted the GO1 task. Unpredictably, on 30% or the trials, the color of the green arrow changed to red, indicating that the GO1 response had to be inhibited and changed (e.g., a left button press had to be stopped and a right button press had to be issued instead). This constituted the STOP and the GO2 task, respectively. This design permitted us to calculate several informative dependent measures of adaptive behavior that were com-

pared between PD and HC groups. First, go RT reflects the latency of initiating an overt choice response to the go signal. Second, we calculated the latency of stopping the go response upon presentation of a stop-change signal (i.e., the SSRT) as an index of inhibitory action control. Based on previous clinical studies, medicated PD patients are expected to show prolonged SSRT compared to HC (Gauggel et al., 2004). Third, change RT was computed as an index of a person's ability to engage an alternative overt action upon the stop-change signal. Fourth, group comparisons were performed with respect to between-trial control adjustments by focusing on response slowing on the go trial that immediately followed a stop-change trial. These sequential effects have been explained in terms of automatic but incorrect retrieval of previously associated stimulus-action goals as well as by adaptive top-down control processes (Verbruggen & Logan, 2008b). In the classical stop task, response latencies are prolonged on a go trial immediately following a stop trial, irrespective of inhibitory success (Bissett & Logan, 2011; Enticott et al., 2009; Rieger & Gauggel, 1999). Interestingly, sequential slowing effects are also evident after successful inhibition, and especially when the go stimulus (e.g., ⬅) repeats on the next trial (e.g., ⬅) compared with the situation in which the alternative go stimulus appears after successful inhibition (e.g., ⬅ followed by ➡; Verbruggen, Logan, Liefooghe, & Vandierendonck, 2008). Here, the go stimulus presented on the inhibited stop trial becomes inadvertently associated with the STOP goal and when the go stimulus repeats on the next trial, the STOP goal is automatically retrieved, thus slowing production of the newly signaled go response (Bissett & Logan, 2011; Logan, 1988; Verbruggen, Logan, et al., 2008; Verbruggen & Logan, 2008b). By investigating sequential effects on performance, we could assess the degree to which PD affects the automatic retrieval of action-goal associations in addition to its effects on initiating, stopping, and changing voluntary movements.

Method

Participants

This study included two groups of participants: 22 individuals diagnosed with PD who were treated with medication and 20 age-matched HC (see Table 1 for demographic information). The two groups did not differ in terms of years of education, $t(40) = 1.12$, $p = .27$; Mini-Mental State Examination (MMSE) score, $t(40) = 1.05$, $p = .30$; age, $t(40) = 0.12$, $p = .91$; or gender distribution, $\chi^2(1) = 0.008$, $p = .93$. Consistent with the prevalence of PD, both samples included a larger proportion of males than females. Participants with PD were recruited from the Movement Disorders Clinics at the University of Virginia and Vanderbilt University and diagnosed with PD by a neurologist specialized in movement disorders. All but one of the PD patients were taking medication to improve dopaminergic function and all were tested during the "on" state of their usual medication cycle. All patients were scored a stage III or below on the Hoehn and Yahr (1967) scale (see Table 1). HC were recruited from the local communities via advertisements in a variety of communication media (e.g., departmental web site, print media).

Dementia was screened using the MMSE. All included participants scored 26 or higher on the MMSE. Depression in the PD sample was quantified with the CES-D (Center for Epidemiological Studies-Depression Scale). Because depression measures contain items that are confounded by physical symptoms of PD, we allowed PD patients scoring higher than 16 to enter the study provided they reported subjectively that mood symptoms of depression were well treated and medical records corroborated this report. The mean CES-D score for PD (see Table 1) was below standard cutoffs suggestive of depressive symptoms. Correlation analysis confirmed that depression measures were unrelated to any of the critical stop task variables of interest (p *values* > 0.12). Patients meeting the following criteria were excluded from study enrollment: untreated and present difficulties controlling depression based on subjective report and corroborated by medical record review, past diagnosis of bipolar disorder or schizophrenia, based on patient report and corroborated by medical record review, untreated diabetes, history of head injury or comorbid neurological condition, history of stroke or cardiac arrest, or major pulmonary disease as reported by participant and corroborated by medical record review.

Table 1
Participant Information

Variable	PD	HC
Sample size (*N*)	22	20
Gender (M:F)	14:8	13:7
Age (years)	66.2 (6.0)	66.0 (6.8)
Education (years)	15.6 (2.6)	14.6 (3.1)
MMSE (raw score)	28.8 (1.4)	29.2 (1.2)
CES-D	15.2 (7.1)	—
Years since PD onset	7.7 (3.4)	—
Age at PD onset	58.5 (6.0)	—
Hoehn & Yahr score	2.0 (.6)	—
Predominant Symptomatology		
Left side (*N*)	3	
Right side (*N*)	5	
Bilateral (*N*)	14	

Note. Standard deviation in parentheses. MMSE = Mini-Mental State Examination; CES-D = Center for Epidemiological Studies-Depression Scale; PD = Parkinson's disease; HC = Healthy control.

All participants had normal or corrected-to-normal vision. Informed consent was obtained prior to participation in the study, in accordance with the Declaration of Helsinki and compliant with standards of ethical conduct in human research as regulated by the local research ethics committee.

Tasks and Procedures

Participants completed the stop-change task in which left- and rightward pointing arrows were presented, one at a time, on a 17-inch digital display monitor placed at a distance of about 90 cm and positioned such that each arrow appeared at eye level (see Figure 2). The go stimulus was a green arrow shown at visual fixation against a white background. It consisted of a rectangular stem (2.1 × 2.1 cm) attached to a triangular arrowhead (1.5 cm height × 2 cm base). Each block of trials began with the appearance of a small fixation square (0.8 cm height × 0.8 cm width, subtending a visual angle of 0.46°) at visual fixation. Green arrows were presented with a variable intertrial interval that ranged randomly from 1,750 ms to 2,250 ms in decrements or increments of 50 ms. The series was structured such that the arrows were

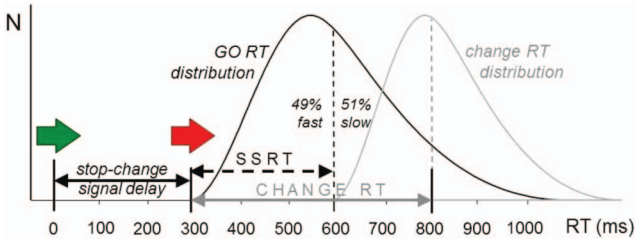

Figure 2. Integration method. Calculation of stop-signal reaction time (SSRT) according to the race model (Logan & Cowan, 1984). The black curve depicts the distribution of RTs on go trials (i.e., trials without a stop-change signal) representing the finishing times of the go process. Assuming independence of the go and stop processes, the finishing time of the stop process bisects the go RT distribution. Given that the response could not be changed successfully on *n* percent of all stop-change trials (here at 49%), SSRT (300 ms) is calculated by subtracting the mean stop-change signal delay (300 ms) from the 49th percentile of go RT (600 ms). The gray curve represents change responses to the stop-change signal. Mean change RT (here 500 ms) is reflected by the latency between stop-change signal delay (300 ms) and change response (800 ms). See the online article for the color version of this figure.

presented pseudorandomly, with the constraint that left- and right-hand responses were signaled equally often within a block of trials. The arrow disappeared from the screen immediately following the participant's response (i.e., a left or right thumb press on a response button located at the end of a grip held comfortably in each hand), or if a time limit of 1,500 ms passed. Participants completed five blocks of 104 trials, the first of which served as a practice block.

Participants were instructed to respond quickly to go signals and not to wait in order to increase their chances of stopping to a stop-change signal. On 30% of the trials, stop-change trials, the green arrow turned red after a variable delay, the change in color serving as the stop-change signal. Upon the color change, participants should inhibit the ongoing go response and execute the opposite response instead. For example, if a green arrow pointing to the right changed to red, participants should issue a left-thumb response instead of a right-thumb response. Because of the possible lateralization of motor symptoms in PD patients, two independent staircase-tracking procedures were implemented for left- and right-hand stop-change trials separately, that dynamically adjusted the interval between the onset of the go stimulus and the onset of the stop-change signal (i.e., the stop-change signal delay) on the next stop-change trial (Levitt, 1971). After successful inhibition of the initial go response, the stop-change signal delay increased by 50 ms, making it more difficult to stop and change on the next stop-change trial. After a failed stop-change trial, the delay decreased by 50 ms making it easier to stop and change. The tracking algorithms ensure that participants can stop and change on approximately half of the stop-change trials, which increases the accuracy of SSRT estimation using the integration method (Band, van der Molen, & Logan, 2003).

Data Analyses

SSRTs to stop-change signals were calculated separately for each subject's left and right hand according to the integration method (Logan, 1994; Logan & Cowan, 1984; see Figure 2). Stop-signal tracking based on inhibition rates of approximately 50% provides stop latency estimates that are relatively insensitive to violations of the assumptions of the race model (e.g., Band et al., 2003; Logan et al., 1997). Change RT is the latency of the change response following the onset of the stop-change signal (see Figure 2).

Because none of the dependent measures differed significantly between left- and right-hand responses (all p values $>.10$), data were collapsed across hands. To compare performance between PD and HC groups, Student's t tests were completed on mean go RT, on SSRT, and on mean change RT for correct trials. Percentages of commission and omission errors on go trials and of stop-change success on stop-change trials were square root transformed before analyses. For analyses of between-trial effects, go trials were categorized according to the within-subject factors (a) Stimulus Sequence, with two levels (repetition trials, e.g., ⬅ followed by ⬅ vs. alternation trials, e.g., ⬅ followed by ➡); and (b) Error Sequence, with two levels (post *go* correct vs. post *go* incorrect). Finally, postchange performance effects following stop-change trials were analyzed using a third factor, Change Success, with two levels (postsuccessful change vs. postfailed change). Because performing multiple tests increases the probability of committing a Type I error, alpha was lowered from .05 to .02 for secondary analyses involving between-trial adjustments.

Results

Go Trials

Mean effects. Although, as shown in Table 2, the overall response latencies of PD to go stimuli appeared to be longer than those of HC (614 ms vs. 578 ms), the difference was not statistically significant, $t(40) = 0.91$, $p = .37$. PD response latencies were more variable than those of HC (PD = 177 vs. HC = 150 ms, $t(40) = 2.20$, $p = .03$) and they made significantly more choice errors than did HC (respectively 5.7% vs. 3.5%, $t(40) = 2.39$, $p = .02$). In contrast, omission errors were similarly low among the two groups (PD = 0.7% vs. HC = 0.4%, $t(40) = 0.65$, $p = .52$).

Alternating versus repeating go trials. As was the case for mean values, response latencies averaged over repeating and alternating go trials were comparable across the two groups (Group: $F < 1$). Overall, responses were 16 ms faster to repeating than to alternating go stimuli (repetition = 558 ms vs. alternation = 574 ms, $F(1, 40) = 6.20$, $p = .02$). However, as is evident in Figure

Table 2
Dependent Behavioral Variables

Variable	PD	HC
Go RT	614 (120)	578 (135)
Choice errors (%)	5.7 (3.8)	3.5 (5.0)
Stop-change signal delay	291 (120)	315 (142)
Failed change RT	554 (117)	501 (90)
Successful stop-change (%)	53 (4)	53 (6)
SSRT*	276 (85)	224 (47)
Change RT*	651 (127)	581 (92)

Note. RT = Reaction time; PD = Parkinson's disease; HC = Healthy control.
* $p < .05$.

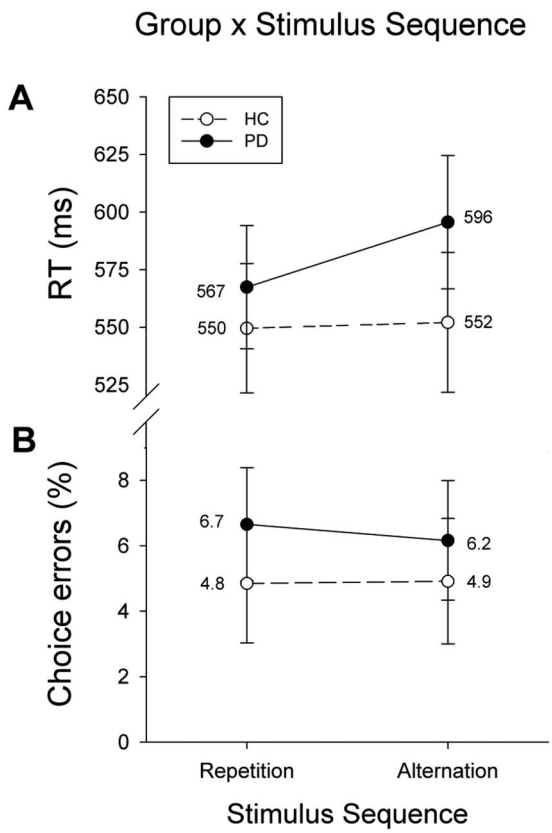

Figure 3. Mean go reaction time (RT) to stimulus repetition and alternation go trials for Parkinson's patients (PD = solid line) and healthy controls (HC = dotted line).

3A, sequential effects differed between the two groups (Stimulus Sequence × Group: $F(1, 40) = 4.32$, $p = .04$). Whereas HC responded equally fast on alternation and repetition go trials (552 vs. 550 ms, $F < 1$), PD experienced a significant cost of 29 ms on alternation as compared to repetition trials (596 vs. 567 ms; $t(21) = 3.54$, $p = .002$).

Similar analyses on choice error rates revealed that accuracy did not differ between the two groups (PD = 6.4% vs. HC = 4.9%, $F(1, 40) = 3.08$; $p = .09$). Responses to alternating go stimuli were slightly less error prone than responses to repetition trials (alternation = 5.5%, repetition = 5.8%, $F(1, 40) = 5.09$, $p = .03$). This pattern, shown in Figure 3B, was equivalent for the two Groups (Group × Stimulus Sequence: $F(1, 40) = 3.08$, $p = .09$).

Posterror slowing. Two HC participants did not make any errors on go trials and were therefore excluded from this analysis. Overall, responses on go trials that followed an erroneous choice response to a go stimulus were about 42 ms slower than responses following a correct go response (Error Sequence: 604 vs. 562 ms; $F(1, 38) = 7.75$, $p = .008$). The magnitude of posterror slowing was comparable among both PD and HC (Group: $F(1, 38) = 1.53$, $p = .22$).

Stop-Change Trials

SSRT. The tracking algorithm worked well. Both groups were able to stop and change their initial go response on 53% of the stop-change trials (Group: $t(40) = 0.37$, $p = .72$). Mean stop-change signal delay did not differ significantly between PD and HC (Group: 291 vs. 315 ms, $t(40) = 0.61$, $p = .54$). As predicted, SSRT was significantly prolonged among PD compared to HC (276 vs. 224 ms; $t(40) = 2.40$, $p = .02$). In line with the predictions of the race model, RT on failed change trials (i.e., responses that escaped inhibition) were shorter than the overall mean go RT (528 vs. 596 ms, $F(1, 40) = 61.19$, $p < .001$). The magnitude of this difference was comparable for the two groups ($F < 1$).

Change RT. PD patients issued the change response significantly slower than HC (Group: 651 vs. 581 ms, $t(40) = 2.04$, $p < .05$). Change RT tended to be more variable in the PD than in the HC group (PD = 136 vs. HC = 114 ms, $t(40) = 1.82$, $p = .08$).

Comparing Go RT, SSRT, and Change RT

Correlations. In the PD group, SSRT was positively correlated with change RT, $r = .69$, $p < .001$, indicating that patients with relatively long SSRT were also slower in executing the alternative change response. The correlations between SSRT and go RT, $r = .18$, $p = .42$ and between go RT and change RT were not significant in the PD group, $r = .29$, $p = .19$.

In the HC group, go RT and change RT were positively correlated, $r = .46$, $p = .04$, indicating that controls who took longer to respond to the go stimulus also took longer to make the alternative response on stop-change trials. In the HC group, the correlation between go RT and SSRT was negative and approached significance, $r = -0.43$, $p = .06$ indicating a slight tradeoff between going and stopping. SSRT and change RT did not correlate in HC, $r = -0.09$, $p = .71$.

ANCOVA. Additional analyses were performed to test group differences in SSRT and change RT in relation to go RT. First, ANCOVA analysis of the group difference in SSRT with go RT entered as a covariate still yielded a significant group effect on SSRT, $F(1, 39) = 5.66$, $p = .02$. This verifies that PD-related slowing in SSRT is independent from and goes beyond group-related variance in go RT. Second, the group effect on change RT was somewhat attenuated after partialing out group-related variance in go RT, $F(1, 39) = 3.22$, $p = .08$. Finally, ANCOVA of group-differences in change RT with SSRT as covariate revealed that the group effect on changing disappeared after partialing out group differences in stopping. $F(1, 39) = 0.88$, $p = .35$. The interdependence between stopping and changing deficits in PD will be interpreted in the Discussion section.

Adjustments Following Go Trials and Stop-Change Trials

Poststop-change versus postgo trials. To investigate between-trial adjustments following stop-change trials, go trials following a stop-change trial were classified according to the within-subject factors Trial Sequence (go trial following a go trial vs. go trial following a stop-change trial) and Stimulus Sequence (go stimulus repetition vs. alternation). Response latencies were significantly longer on go trials that immediately followed a stop-change trial rather than following another go trial (698 vs. 566 ms, trial sequence: $F(1, 40) = 202.52$, $p < .001$). Similarly, response latencies tended to be longer to alternations than to repetitions of the go stimulus (638 vs. 627 ms; Stimulus Sequence: $F(1, 40) =$

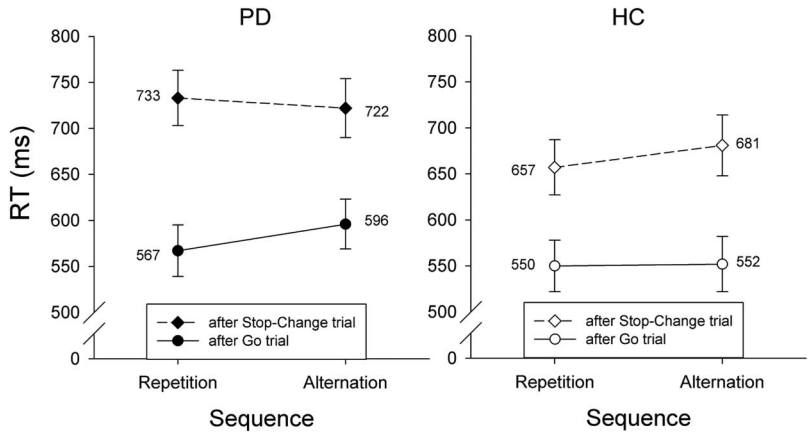

Figure 4. Mean reaction times (RTs) for correct go trials as a function of *Trial Sequence* (after a go trial vs. after a stop-change trial) and *Stimulus Sequence* (repetition vs. alternation). For alternation trials, the magnitude of post-stop-change slowing is comparable for Parkinson's patients (PD) and healthy controls (HC). Patients show increased slowing, however, on go trials following stop-change trials when the go stimulus repeated.

3.76, $p = .06$). Interestingly, as illustrated in Figure 4, response latencies for both PD and HC on go trials increased following a stop-change trial, but the magnitude of this slowing differed between the two groups as a function of whether or not the go stimulus was repeated (Trial Sequence × Stimulus Sequence × Group: $F(1, 40) = 8.82$, $p = .005$). When go stimuli alternated, the slowing was comparable in magnitude for the two groups (126 vs. 129 ms, $F < 1$). However, when a go stimulus was repeated after a stop-change trial, PD slowed more than HC (166 vs. 107 ms, $F(1, 40) = 7.32$, $p = .01$). Apparently, PD have greater difficulty decoupling a go stimulus association with a stop-change goal; hence, the longer RT to a repeated go stimulus following a stop-change trial with the same go signal.

Adjustment following successful change versus failed change. We assessed the effect of change success on response latency on the subsequent go trial using the within-subject factors Change Success (go trials following a successful change vs. following a failed change trial) and Stimulus Sequence (go stimulus repetition vs. alternation). Overall, response latencies to the go stimulus following a successful change were prolonged compared to go trials following a failed stop-change trial (respectively 752 vs. 647 ms, Change Success: $F(1, 40) = 107.54$, $p < .001$). This difference was comparable among PD and HC (119 vs. 90 ms; Change Success × Group: $F(1, 40) = 2.14$, $p = .15$).

However, the direction of the effect reversed when the go stimulus was repeated as opposed to when the go stimuli alternated (Change Success × Stimulus Sequence: $F(1, 40) = 32.21$, $p < .001$). Following successful change trials, responses to go stimulus repetitions were 67 ms *faster* than responses to go stimulus alternations, $F(1, 42) = 32.66$, $p < .001$. Conversely, following failed change trials, responses to go stimulus repetitions were 43 ms *slower* than responses to go stimulus alternations, $F(1, 42) = 10.78$, $p = .002$. In Figure 5 it is evident that this pattern was obtained among both PD and HC (Change Success × Stimulus Sequence × Group: $F(1, 40) = 1.60$, $p = .21$). Apparently, both HC and PD have difficulty decoupling the association between the successfully changed-to response and the stop-change goal; hence, the longer RT to an alternating go stimulus following a successful stop-change trial.

Similar analyses were performed on choice errors made on go trials that occurred after successful and after failed change trials (see Figure 6). On average, more choice errors were committed on go trials following successful compared to following failed change trials (13.8% vs. 5.4%, Change Success: $F(1, 40) = 49.44$, $p < .001$), with both groups being equally sensitive to this effect (Change Success × Group: $F < 1$). Overall, errors were more likely when the go stimulus alternated than when the go stimuli repeated (13.6% vs. 5.7%, Stimulus Sequence: $F(1, 40) = 21.83$, $p < .001$), and the size of the difference was comparable among PD and HC (Group × Stimulus Sequence: $F(1, 40) = 2.34$, $p = .13$). Interestingly, the combined relationship between change success and go stimulus repetition or alternation differed between the two groups (Change Success × Stimulus Sequence × Group: $F(1, 40) = 4.39$, $p = .04$). To break down this three-way interaction on error rates, we analyzed the effect of go Stimulus Sequence (repetition vs. alternation) separately for go trials following a successful change versus after a failed change trial. After a failed change trial, error rates were higher for go stimulus repetitions than for alternations, $F(1, 40) = 4.36$, $p = .04$. The magnitude of this sequence effect on error rates was comparable between groups ($F < 1$). Alternatively, after successful changing, the effect of stimulus sequence reversed: More errors were committed for go alternations than for repetitions, $F(1, 40) = 68.20$, $p < .001$. However, the costs for alternations were much more pronounced in PD compared with HC (24.6% vs. 13.8%, Stimulus Sequence × Group: $F(1, 40) = 6.61$, $p = .02$). This error pattern indicates that PD patients, more than HC, have difficulty decoupling the association between the successfully changed-to response and the stop-change goal; hence, the higher error rates to an alternating go stimulus following a successful stop-change trial.

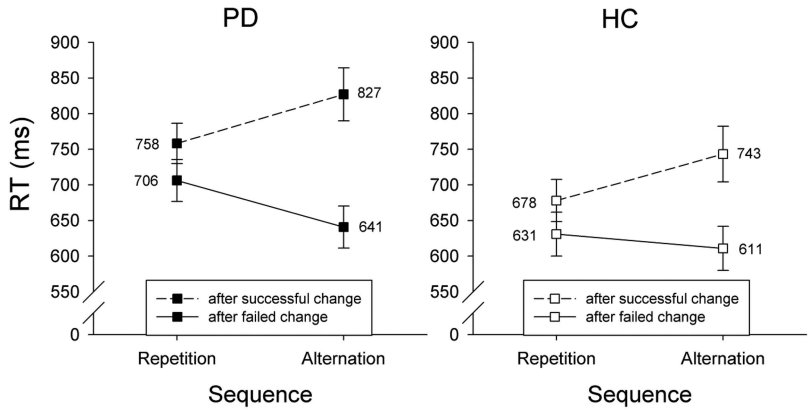

Figure 5. Mean reaction time (RTs) for correct go trials as a function of *Change Sequence* (previous trial was a successful change vs. failed change) and *Stimulus Sequence* (repetition vs. alternation). Following successful change (dotted lines), responses to repetition trials were faster than to alternation trials. However, following a failed change trial (solid lines), responses were faster on alternation than repetition trials. Patients (PD = left panel) and healthy controls (HC = right panel) showed a similar pattern of postchange trial adjustments in response latency.

Discussion

This study centered on the ability to override motor actions by comparing performance of medicated PD patients and HC on the stop-change task. Our goals were to make group comparisons with respect to (a) the proficiency of stopping control over voluntary actions, (b) the ability to flexibly change behavior by executing an alternative motor response, and (c) the ability to decouple stimulus–response associations or to resolve incorrect response activation.

PD is Associated With Slower Stopping

The go signals used in the present task were centrally presented arrows that conveyed spatial information with respect to the correct go response. Overall, response latencies to go signals did not differ significantly between the two groups (see also Gauggel et al., 2004). That is, PD patients were as fast as HC generating an overt motor action in response to external signals that provide corresponding spatial information about the correct response hand. Despite comparable response latencies to the go signal, responses made by the PD group were characterized by increased variability. Although go responses were generally very accurate, the PD group committed more choice errors relative to the controls, suggestive of qualitative differences in the response execution process in PD compared with HC (see also Gauggel et al., 2004). These findings indicate that both groups performed well on the primary task of the stop-change paradigm.

The most interesting trial category consisted of stop-change trials. Here, participants tried to inhibit their go response and to execute the alternative action instead. When confronted with the

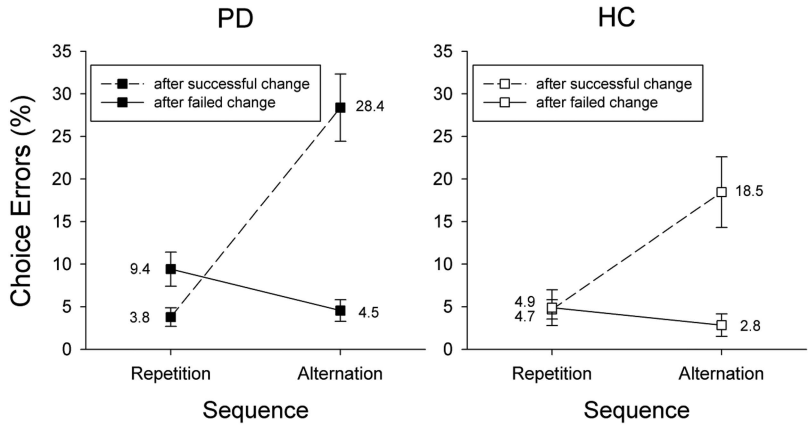

Figure 6. The percentage of errors on go trials as a function of variations in *Change Sequence* (previous trial was a successful change vs. failed change) and Stimulus Sequence (repetition vs. alternation trial). Go trials following successful change (dotted lines) were more prone to errors, but only when the go stimulus alternated. Patients (PD = left panel) were more sensitive to this sequential effect on error rates compared to healthy controls (HC = right panel).

stop-change signal, stopping the ongoing but unwanted action is an essential and initial element of goal-directed action control. In this sense, the stop-change task used in the present study is an elaborated version of the standard stop-signal paradigm (Logan, 1994; Logan & Cowan, 1984). As predicted, group comparisons of SSRT indicated significantly prolonged stopping latencies in PD patients compared with HC. The notion of a PD-related stopping deficiency is in line with previous clinical studies that used the standard version of the stop-signal task (Gauggel et al., 2004). Correlation analyses revealed that HC who responded relatively slower to go signals, tended to inhibit faster. This might be indicative of strategic adjustments made to balance going and stopping performance in the stop-change task. Interestingly, no such trade-off between going and stopping was observed in PD.

The current findings contribute to the mounting evidence linking basal ganglia function and dysfunction to variations in inhibitory motor control (Alexander et al., 1986; Aron, 2007; Hikosaka, 1998; Mink, 1996; Mink & Thach, 1993; Redgrave et al., 1999; Robbins & Brown, 1990). In fact, the current findings combined with other similar results highlight the intriguing pattern that the generation of fast choice reactions in PD are often indistinguishable from age peers (Bissett et al., 2015; Gauggel et al., 2004). Therefore, PD may involve a more fundamental disruption of the ability to inhibit actions, which in turn compromises the initiation of subsequent movements. Thus, the problems typically described with movement initiation and execution in PD may be more fundamentally related to the consequences of impaired inhibition rather than to impaired response initiation to external cues per se.

PD is Associated With Slower Changing

The benefit of the stop-change task over the standard stop paradigm is that it allows investigating the proficiency to override overt actions by executing an alternative motor response. The stop-change signal not only signals the inhibition of the ongoing go response, but also instructs the participant to generate the alternative action. A dynamic tracking algorithm controlled the onset of the stop-change signal such that the stop-change signal delay was continuously adjusted as a function of individual stop-change success. Despite the finding that both groups showed comparable go RT, the PD group was significantly slower (i.e., by 70 ms) in issuing the change response than the control group. This indicates a specific impairment among medicated PD patients in flexibly activating alternative actions when signaled to do so. This finding is interesting given that overt response latencies to the go signal did not differ significantly between the two groups. Apparently, PD differentially affects issuing an alternative change response that overrides the initial action, while leaving intact the ability to initiate a response to isolated symbolically compatible go signals.

The present pattern of results shares a resemblance with performance of PD patients on conflict tasks that measure the ability to resolve the conflict between action tendencies (for a review, see van den Wildenberg et al., 2010). Response latencies to nonconflict stimuli are often indistinguishable in PD compared with HC (Praamstra et al., 1998), much like HC and PD patients responded equally fast to go trials in the stop-change task in the present study. However, PD is associated with higher interference (i.e., RT slowing) on conflict trials, exposing a deficit in engaging a correct response due to poor inhibition of the incorrect response tendency (Praamstra et al., 1998; van Wouwe et al., 2016; Wylie, Ridderinkhof, Bashore, et al., 2010). In a way, a stop-change trial can be viewed as a particular instance in which two alternative and mutually exclusive response tendencies are simultaneously activated, as on a conflict trial, which slows the execution of the goal-directed change response in PD compared with the HC group.

A distinct pattern emerged with respect to the relation between going, stopping, and changing.

In HC, go RT and change RT correlated positively, indicating that controls who were faster to respond to the go signal were also relatively faster to respond to the change signal. This pattern suggests that for HC, similar action generation mechanisms may be at play for responding to go signals and to change signals. Interestingly, change RT did not correlate with go RT in PD. Instead, a significant correlation was obtained between change RT and SSRT. PD patients who stopped relatively slowly were slower to issue the change response, suggesting that the change latency may depend on stopping latency. In addition, the change deficit in PD related to the inhibitory deficit, because the group effect in change RT disappeared after partialing out group-differences in SSRT.

These disparate group patterns with respect to the relations between the various dependent RT variables may be interpreted meaningfully in terms of the cognitive architecture underlying stop-change signal processing. Verbruggen and colleagues proposed two alternative processing models that might explain stop-change behavior (Verbruggen & Logan, 2008b). The absence of a correlation between stopping and changing in HC is in line with the limited-capacity model that describes parallel activation of these processes (i.e., the stop and the change process run simultaneously). In contrast, the dependency between stopping and changing observed in the PD group may reflect a processing architecture that postulates nondeterministic serial activation. According to this model, stopping has to complete before executing the change response. Therefore, the onset the change process depends on the finish of the stopping process, creating a dependency between these two (serial) processes in the PD group.

Performance Adjustments Following Change Trials

The stop-change paradigm offers the opportunity to investigate behavioral adjustments based on trial sequence. Using the classical stop-signal paradigm, Verbruggen and Logan (2008b) found that go signals occurring on stop trials become associated with stopping. If the go signal repeats on the subsequent trial, participants retrieve the stop association, which slows responding. In line with this *memory hypothesis*, Bissett and Logan (2011) observed that HC slowed their responses on go trials directly following a stop-signal trial. This poststop slowing was larger if the go signal repeated compared with when it alternated.

We investigated if experience modulates behavior differently in PD than in HC by comparing behavior following a change trial. Consider a stop-change trial presenting a green go arrow pointing right, followed shortly by a color change signaling the need to stop and change actions. The correct action is to inhibit the right-hand response and to press left. Suppose the participant was successful in stopping and changing the go response; thus, (s)he successfully inhibited the right go response and correctly executed the left

response. According to the memory hypothesis, the right arrow stimulus presented on the stop-change trial becomes associated with the "change goal." Automatic retrieval of the associated "change goal" should cause slower responses to repeating go signals. However, the present sequential data are not in line with this prediction. In contrast, we observed that both PD and HC respond slower and make more errors when go signals alternated rather than repeated. Apparently, on stop-change trials, it is not the go *stimulus*, but the swapped-to *response* that becomes associated with the "change goal." Thus, on a successful stop-change trial with an arrow pointing right, the overt change response (i.e., left-hand button press, or "action representation left") will become associated with the "change goal." A subsequently presented (alternating) go arrow pointing left then triggers the action representation "left," inadvertently leading to the retrieval of the recently associated "change goal." This retrieval process on alternations interferes with the execution of the correct left-hand response, making it slower and more prone to decision errors. This liberal extension of the memory hypothesis is in line with the feature binding account proposed by Hommel (2004), suggesting that the integrating and binding of features spans codes that represent perceived events (such as stimuli) and produced events (such as performed actions).

The principle of the automatic retrieval of previously formed but detrimental associations between action codes and goal representations can also explain the aftereffects observed following failed-change trials. If changing was unsuccessful, the "change goal" conveyed by the color change will be associated with the action code related to the executed response. For example, a right-hand response on a failed stop-change trial forms an association between the action representation "right" and the "change goal." If the right go arrow repeats, the automatically retrieved "change code" will interfere, thereby slowing the right-hand response. When presented with an alternating (in this case left-pointing) go arrow, activation of the code "left" is not associated with the "change goal," thus precluding aftereffects; hence, RT is relatively short. This pattern of relatively fast go responses to alternated go signals following failed-change trials is exactly what we observed.

Sequential effects on performance following change trials reflect the influence of automatically retrieved associations between action representations and goal representations. This interpretation is a version of the original event-file theory (Hommel, 1998) and requires a last-in first-out rule, meaning the retrieval of the last stimulus-response episode. In both HC and PD groups, the automatic retrieval of action and goal associations had a detrimental effect on (alternating) go RT following a successful change. Interestingly, on these alternated go trials following successful change, PD patients committed a disproportionately large amount of incorrect reversals (i.e., 28%) compared with controls. This high error rate likely reflects a PD-related inability to override, or unbind, previously formed associations between action and goal representations. Thus, the costs incurred indirectly by a recent override may result from the need to unbind the now-counterproductive associations between the overt response and the "change goal." However, these costs may also result from the actual *activation* of the incorrect response as driven by the preceding action-goal association. In this case, it would be the incorrect response activation, and the need to resolve the ensuing response conflict, that produced the cost. Because the present data do not allow conclusions to be drawn about whether the feature unbinding account, the response activation account, or both hold merit, future studies are needed to test these speculative accounts of the aftereffects of action override. Either way, the present clinical results are consistent with the notion that both the proficiency of inhibitory control over actions (Alexander et al., 1986; Aron, 2007; Hikosaka, 1998; Mink, 1996; Mink & Thach, 1993; Redgrave et al., 1999; Robbins & Brown, 1990) as well as feature binding of stimulus and response codes are linked to basal ganglia functioning and the integrity of dopaminergic pathways (e.g., Colzato et al., 2012).

Limitations

In the current task, the alternative response consisted of executing a button-press with the hand not indicated by the go arrow. Thus, upon presentation of a stop-change signal, participants have to process the directional information conveyed by the go signal in order to change their initial go response into the alternative change response. This setup might have induced a dependency between going and stopping, thereby violating an important assumption of independence of the race model that underlies performance on the stop task (Logan, 1994; Logan & Cowan, 1984). However, our finding that responses are slower on failed change trials than on go trials in both groups supports the notion that the independence assumption was not violated and that SSRT estimates are reliable. To circumvent issues of dependence between going and stopping, future investigations of change behavior might instruct participants to issue an alternative change response with their feet or with fingers that is not part of the response set of the go task.

PD patients were tested on medication. An extant issue unresolved in the current study is the extent to which dopamine medications impact performance in the PD group. A straightforward approach would be to test patients withdrawn and taking their dopamine modulating medications. To our knowledge, just one study has investigated stopping speed in PD patients on and off dopamine medications, finding no statistically significant modulation of SSRT with Levodopa medication (Obeso, Wilkinson, & Jahanshahi, 2011). However, a variant of the stop-signal task was used that required conditional stopping, observing task performance that violated key assumptions of the horse race model (i.e., response latencies on failed stop trials were not shorter compared with mean go reactions). A future investigation of dopamine medication effects using a more conventional stop task or stop-change task would be most informative.

The present study did not distinguish between clinical subtypes of PD. Classification in terms of predominant diagnostic motor symptoms yields three phenotypes; tremor dominant (TD), akinetic-rigid (AR), and a subtype characterized by postural instability and gait disorder (PIGD; Nutt et al., 2011; Paulus & Jellinger, 1991). Studies using conflict paradigms indicated that PIGD patients made significantly more impulsive motor errors than did TD patients (Vandenbossche et al., 2012; Wylie, van den Wildenberg et al., 2012). This indicates that PIGD is associated with greater susceptibility to acting on externally driven motor impulses. A specific clinical motor symptom, namely freezing of gait (FOG), seems to be associated with impaired action control. Both patients with and without FOG show impaired stop-signal inhibition relative to controls (Bissett et al., 2015). However, those patients experiencing FOG slowed their go responses twice as much as patients without FOG, suggesting a greater trade-off

between going and stopping in FOG (see also Tolleson et al., in press). Future studies might compare the ability to stop and change between PD subtypes.

Conclusion

The present findings indicate that PD patients need more time to stop their motor actions to external stopping cues than HC. After successfully aborting their initial action, PD patients are also slower to issue an alternative action, indicating a deficit in the proficiency of changing their motor actions. The changing deficit in PD related to the inhibition deficit. This is in line with a serial processing architecture. In PD, stopping had to finish before the change response could be initiated, whereas HC performance was characterized by parallel stop and change processing. Finally, trial-by-trial analyses indicated that aftereffects of changing entail costs in terms of response slowing and decision errors, especially among PD patients, that are driven by the impaired ability to decouple action-goal associations and/or the impaired ability to resolve incorrect response activation. These behavioral data support the notion that both higher-order cognitive control functions (i.e., response inhibition and action override) and lower-order feature binding mechanisms link to the integrity of the basal ganglia.

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