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Impulsive oculomotor action selection in Parkinson's disease

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Abstract

The effects of Parkinson's disease (PD) on the dynamics of impulsive action selection and suppression have recently been studied using distributional analyses, but with mixed results, especially for selection. Furthermore, some authors have suggested that impulsivity,

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regarded as a personality trait, shares common features with behavioral tasks' measures. The current study was designed to clarify the impact of PD on impulsive action selection and suppression, and investigate the link between cognitive action control and self-reported impulsivity. We administered an oculomotor version of the Simon task to 32 patients with PD and 32 matched healthy controls (HC), and conducted distributional analyses in accordance with the activation-suppression model. Patients and HC also filled out the Barratt Impulsiveness Scale (BIS) questionnaire. Results showed that patients with PD were faster overall and exhibited a greater congruence effect than HC. They also displayed enhanced impulsive action selection. By contrast, the suppression of impulsive responses was similar across both groups. Furthermore, patients had higher impulsivity scores, which were correlated with higher impulsive action selection and higher suppression. Our study yielded two interesting findings. First, PD resulted in a higher number of fast errors. The activation-suppression model suggests that patients with PD are more susceptible to the impulsive action selection induced by the irrelevant stimulus dimension. Second, impulsive action selection and suppression were both associated with trait impulsivity, as measured by the BIS, indicating that these two aspects of impulsivity share common features.

Keywords: Cognitive action control; Parkinson's disease; Impulsivity; Activation-suppression; Simon task

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1. Introduction

Efficient cognitive control is vital when a choice has to be made between strong response alternatives. One of the underlying functions of cognitive control, the online resolution of conflict situations, also known as *cognitive action control*, has been extensively

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studied. Experimental tasks that put the participants in a situation of conflict between two response alternatives typically show that conflict resolution has a cognitive cost. One of the most widely used conflict-inducing paradigms is the Simon task (Simon and Berbaum, 1990). In this task, participants have to press a button according to the color of a circle displayed on either the right- or lefthand side of a screen. In incongruent situations, the color of the stimulus and its display side activate opposite responses, while in congruent situations, both items of information trigger the same response. Simon task studies have repeatedly shown that incongruent situations lead to an increase in reaction times (RTs), reflecting the so-called *Simon effect* or *congruence effect*, and a decrease in accuracy (Hedge and Marsh, 1975; Simon, 1969; Simon and Berbaum, 1990; Van der Lubbe and Verleger, 2002; Wöstmann et al., 2013).

The congruence effect is usually explained by dual-route models, which posit that response activation can follow two parallel routes: an automatic one and a controlled one (Kornblum et al., 1990). According to this view, the automatic route favors the expression of overlearned actions, while the controlled route fosters intention-driven behavior. Thus, during conflict tasks, the irrelevant dimension of the stimulus triggers a fast response through the automatic route, while the relevant dimension triggers a slower, goal-directed response through the controlled route. Accordingly, in the congruent situation, the automatic and controlled routes both support the same response, leading to response facilitation. In the incongruent situation, however, the two routes activate contrasting motor programs, and the individual must be able to suppress the automatic response activated by the irrelevant information in favor of the goal-directed one.

A recent model of cognitive action control refined the dual-route hypothesis by distinguishing between the processes of response selection and suppression. The activation-suppression model suggests that a selective inhibition mechanism is set up to

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suppress the inappropriate activation elicited by the irrelevant stimulus dimension (Ridderinkhof, 2002). However, this selective inhibition takes time to build up. As a consequence, the inappropriate automatic activation is hard to suppress immediately after stimulus presentation. The fastest responses in the incongruent situation are therefore more error prone. This has been highlighted using conditional accuracy functions (CAFs), which display accuracy as a function of the RT distribution divided into bins. The fastest responses (those in the first bin) are thought to reflect automatic activation by the irrelevant dimension, with a higher number of fast errors in the incongruent situation indicating more impulsive action selection. As the selective inhibition of this impulsive action selection takes time to become effective, we can assume that the inappropriate activation is more efficiently suppressed when responses are slow. This assumption is supported by delta plots describing the congruence effect (incongruent RTs minus congruent RTs for correct responses) as a function of RT distribution. Simon task delta plots typically show a decrease in the congruence effect as RTs increase, and the slope between the last two bins is thought to reflect the strength of the selective inhibition process, with a steeper negative slope corresponding to stronger inhibition (see van den Wildenberg et al., 2010, for a review). The fast error rate in CAFs and the strength of the last slope in the delta plots are increasingly being used as parameters to assess impulsive action selection and suppression in both healthy and pathological populations (Castel et al., 2007; Juncos-Rabadán et al., 2008; Proctor et al., 2005; Van der Lubbe and Verleger, 2002; Wylie et al., 2009a).

Cognitive action control is mostly supported by a prefrontal-basal ganglia network (see Ridderinkhof et al., 2011, for a review). More specifically, the pre-supplementary motor area (pre-SMA), which is part of the supplementary motor complex, the inferior frontal cortex (IFC), and the subthalamic nucleus (STN) are all thought to play a major role in impulsive action selection and suppression. The STN is thought to share direct connections with the pre-

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SMA and the IFC, forming a network that supports conflict resolution (Aron et al., 2007; Majid et al., 2013; Mink, 1996). For instance, a study focusing on the effect of deep brain stimulation of the STN in patients with Parkinson's disease (PD) revealed that electrical stimulation of the STN results in more impulsive action selection and enhanced late selective inhibition (Wylie et al., 2010b). The role of the STN in inhibitory control has also been confirmed by direct recordings in patients with PD, which have revealed changes in activity relative to stopping performance in a stop signal task (Alegre et al., 2013), and by the study of PD patients who underwent subthalamotomy (Obeso et al., 2014).

Since cognitive action control relies on prefrontal-basal ganglia networks, we would expect diseases that affect these brain networks, such as PD, to hinder its efficiency. Most of the studies that have investigated cognitive action control so far have found that conflict resolution is indeed impaired in patients with PD, as indicated by a higher congruence effect (Brown et al., 1993; Praamstra et al., 1999, 1998; Praamstra and Plat, 2001; Schmiedt-Fehr et al., 2007; van Wouwe et al., 2014; Wylie et al., 2005), although some studies have failed to observe this effect (Cagigas et al., 2007; Falkenstein et al., 2006; Lee et al., 1999). This impairment has been shown to depend on dopaminergic treatment (van Wouwe et al., 2016) and disease characteristics such as motor symptom severity (Vandenbossche et al., 2012, 2011; Wylie et al., 2010a). However, very few studies have investigated the effect of PD on the dynamics of cognitive action control as proposed by the activation-suppression model. Most of these studies assessed PD patients with dopaminergic medication and their results are somewhat inconsistent. Although most of them describe impaired selective inhibition in patients, revealed by a less negative final delta-plot slope (van Wouwe et al., 2014; Wylie et al., 2010a, 2009a, 2009b), the effect of PD on impulsive response selection is unclear. For example, when Wylie et al. (2009a) used a flanker task to assess medicated patients with PD, they found that patients exhibited a greater congruence effect than HC, and stronger impulsive

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response selection, as revealed by a lower accuracy rate for the first CAF bin. In a subsequent study, however, they failed to demonstrate an increased congruence effect or increased susceptibility to response capture, except in patients with the most severe motor symptoms (Wylie et al., 2010a). The reasons for such mixed results are uncertain. It is possible that heterogeneity in the experimental methods might play a role. For example, Wylie et al. have used an Eriksen flanker task (2009) then a Simon task (2010) and observed different results. This could be explained by the nature of the stimuli, known to influence the strength of the conflict (Wascher et al., 1999; Mattler et al., 2003). It is also possible that heterogeneity in the patients' characteristics might have influenced the performance. For instance, Wylie et al. (2010) showed that the severity of the motor symptoms had an impact on the amount of fast errors. Among the studies investigating the effect of PD on the dynamics of cognitive action control, only one assessed PD patients without dopaminergic medication (van Wouwe et al., 2016). This study revealed no difference between patients without medication and healthy controls in impulsive action selection. While this suggests that there is no pure PD effect on impulsive action selection, it remains unclear whether PD patients with their usual medication are impaired or not in this process. It therefore remains unclear whether patients with PD display greater impulsive action selection.

Patients with PD have been shown to be faster than HC in the oculomotor response modality, and oculomotor versions of the Simon task have been found to yield more errors than manual versions (Fielding et al., 2005; Sullivan and Edelman, 2009). We suggest that most errors in the oculomotor tasks are fast errors, as predicted by the activation-suppression model, and that oculomotor versions of the Simon task are more useful for gauging impulsive action selection. We therefore hypothesized that if patients with PD are characterized by greater impulsive action selection, an oculomotor version of the Simon task is more likely to bring it to light. We also chose to use the oculomotor modality as there is a great amount of

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studies on the impact of PD on saccades performances that may, in part, rely on impairment in cognitive action control. For example, PD usually impairs volitional saccades (slowing RT and decreasing accuracy, see Terao et al. 2013 for a review) while visually-guided saccades are relatively spared. Furthermore, investigating conflict effect on eye movements has an important implication regarding the ability to ignore irrelevant stimuli from the environment and favor relevant ones. This is of major interest in PD as these patients have been shown to be more attracted than controls by irrelevant visual stimuli (Deijen et al., 2006, van Stockum et al., 2011) .The first objective of the current study was thus to confirm this effect of PD on cognitive action control using an oculomotor version of the Simon task that has yielded results consistent with the activation-suppression model in healthy controls (Duprez et al., 2016). We hypothesized that if PD results in greater impulsive action selection, it would increase the number of fast errors in CAF.

Our second objective was to investigate the relationship between cognitive action control abilities and impulsivity, treated as a personality trait. More specifically, we wondered whether there is a link between impulsive action selection and suppression in conflict tasks such as the Simon task and self-reported impulsivity. Some studies have reported inconsistent results regarding the potential link between different measures of impulsivity (Aichert et al., 2012; Caswell et al., 2015). The activation-suppression model allows for the investigation of impulsive action selection and suppression, and we argued that this link appears when focusing on the first CAF bin or last delta-plot slope. We therefore sought to evaluate the link between self-reported impulsivity, as assessed by the BIS-10 questionnaire (Baylé et al., 2000), and the dynamics of cognitive action control in patients with PD and HC. More specifically, we sought to investigate the relationship between the total score and cognitive and motor subscores on the questionnaire and the processes of impulsive action selection and suppression. To this end, we conducted correlation analyses between BIS-10 scores and

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measures of the fastest responses in conflict situations, as reflected by the first CAF bin, and the steepness of the last slope of the delta plot. We predicted that distributional analyses would reveal a link between the number of fast errors, the steepness of the last delta-plot slope, and the BIS-10 scores. This link would indicate that higher impulsivity scores are associated with more impulsive action selection and impaired selective inhibition in both HC and patients with PD.

2. Methods

2.1. Participants

Thirty-two HC and 32 patients with idiopathic PD (Hughes et al., 1992) took part in this study (Table 1). They did not significantly differ on age, sex or education. The patients with PD were recruited from the Neurology Department of Rennes University Hospital (France). All patients had mild to moderate disease severity (Stages I-III in the on-medication state; Hoehn and Yahr, 1967) and were free from all other neurological or psychiatric pathologies, including impulsive-compulsive disorders. They all had a Mattis Dementia Rating Scale (MDRS) score > 130 that excluded dementia (Mattis, 1988). The severity of their motor symptoms was assessed using the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-III). All patients were on dopaminergic replacement medication and were assessed in their on-medication state for all parts of the experiment. Five patients were on levodopa only, one was on dopamine agonists only, and 26 were on both levodopa and dopamine agonists. All the healthy participants underwent an extensive interview to ensure that they had no history of neurological or psychiatric pathology, and no recent drug use. All participants, including patients, had normal or corrected-to-normal vision and gave their written informed consent. They all completed the BIS-10 questionnaire (Baylé et al., 2000). This study was conducted with the approval of the local ethics committee of Rennes

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University Hospital and in accordance with the Declaration of Helsinki and current French legislation (Huriet Act).

Table 1 Demographics, clinical scores and Simon task data for the PD and HC groups

	HC (n = 32)	PD (n = 32)	p value
Age (years)	55.5 (8.9)	58.7 (9.8)	0.1
Education (years)	13.5 (2.7)	13.1 (3.2)	0.47
Sex (M:F)	10:22	18:14	0.08
Disease duration	-	9.5 (4.1)	-
Hoehn and Yahr rating-ON	-	1.1 (0.8)	-
Hoehn and Yahr rating-OFF	-	2.7 (2.3)	-
UPDRS-motor subscore-ON	-	11.2 (8.9)	-
UPDRS-motor subscore-OFF	-	32.3 (12)	-
LEDD (mg)	-	995.4 (316.4)	-
MDRS	-	139.2 (3.8)	-
BIS	45.4 (11.8)	44.3 (11.7)	0.7
Simon task			
Congruent			
RT (ms)	416.2 (118.6)	367.2 (143.6)	
Accuracy (%)	92.7 (25.9)	90.8 (28.8)	
Incongruent			
RT (ms)	450.2 (101.7)	440.1 (123)	
Accuracy (%)	78.7 (40.9)	60.9 (48.8)	
Simon effect			
RT (ms)	34.6 (45.5)	74.4 (61.4)	
Accuracy (%)	14.3 (17.5)	28.9 (27.3)	

Note. Standard deviations shown in parentheses. LEDD = levodopa equivalent daily dose.

2.2. Task design and procedure

The Simon task was designed using MeyeParadigm® software (Version 1.18, e(ye)BRAIN). Participants sat 60 cm away from a 22-inch screen and performed the whole task in darkness. The screen was positioned so that the stimuli appeared at eye level. The stimulus was a blue or yellow square (0.6 x 0.6 cm) displayed at a 12° visual angle on either the left- or righthand side of the screen (Fig. 1). Responses were saccadic eye movements made to the left or right.

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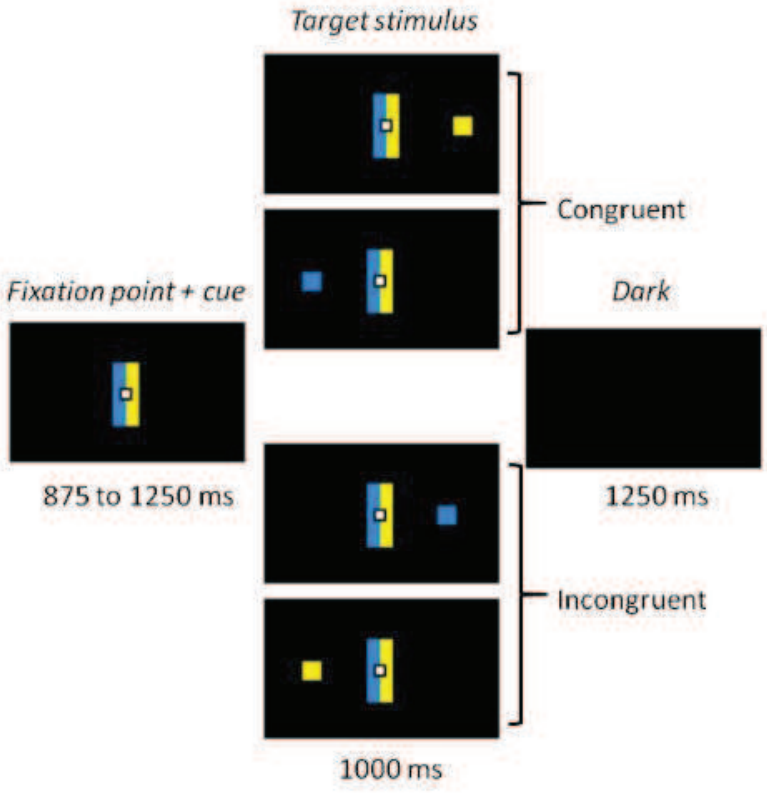


Figure 1: Experimental task. Participants had to make a left or right eye movement according to the color of the target stimulus, ignoring its location. Rectangular cues flanking the fixation point held the color-response mapping constant. When the side indicated by the color matched the location of the target, the trial was congruent. When color and location did not match, the trial was incongruent.

Each trial began with the display of a central white square (0.6 x 0.6 cm) that served as a fixation point for 875–1250 ms (125-ms pseudorandom steps). It was flanked by two contiguous rectangular cues (5 x 1 cm), one blue one yellow (Fig. 1). The target stimulus was then displayed on the left or right side of the screen for 1000 ms. The trial ended with a black screen displayed for 1250 ms before the next one started.

The color side of these cues was randomly reversed across participants. The targets were displayed randomly, with an equal number of 2 (color) x 2 (location) combinations. The task began with a 16-trial practice block and was followed by an experimental phase containing 300 trials divided into five blocks, each containing 60 trials. The blocks were separated by short breaks to avoid tiredness.

2.3. Eye movement recording and data analysis

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Eye-movements were recorded with a head-mounted eyetracker (EyeBrain T2®, e(ye)BRAIN®). Horizontal saccades were recorded at a 300 Hz sampling rate and an angular resolution of 0.5°. Saccade RTs and accuracy were analyzed off line with MeyeAnalysis® software (e(ye)BRAIN®). Saccade detection was based on an algorithm adapted from Nyström and Holmqvist (2010). The first saccade after stimulus presentation was taken to be the participant's response and was counted as correct when it corresponded to the side indicated by the color of the target stimulus. We excluded all saccades with an amplitude below 2° (to discard micromovements around the fixation point), a latency below 100 ms (corresponding to anticipated responses; see Leigh and Zee, 1999) or above 1000 ms (corresponding to target duration), and outlier latencies more than three standard deviations from the mean RT. We removed 1.4% of the whole dataset from the analyses with these parameters. Mean RTs for correct trials and accuracy scores were calculated for each group and each congruence condition, to assess the effect of group on the congruence effect. We further analyzed the data with distributional analyses, in accordance with the activation-suppression model (Ridderinkhof, 2002). First, we used CAFs displaying accuracy as a function of RT to assess automatic response activation. To do this, we plotted accuracy levels against the RT distribution for each congruence condition and by group. For each participant, RTs were rank-ordered and split into seven bins containing an equal number of trials, and mean accuracy was then plotted for each bin. Second, we created delta plots to assess the dynamics of selective suppression. We plotted the mean congruence effect (incongruent RT minus congruent RT for correct trials) against RT distribution, which we then split into seven bins, as we did for the CAFs.

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2.4. Statistical analysis

Data management and statistical analyses were performed using R© software (Version 3.1.0) implemented with the nlme (José Pinheiro (S version) et al., 2014) and lme packages (Bates et

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al., 2014). RTs were compared between congruence conditions and groups using a linear mixed model considering congruence and group as fixed effects and a random participant effect. As accuracy is a binary parameter, we used a nonlinear mixed model with the same fixed and random effects. We chose to use these models because they allowed us to work on the whole dataset, thus avoiding the loss of power that comes with averaging data. They also allowed us to take interindividual variability and unbalanced data into account (see Gueorguieva and Krystal, 2004). The CAF analysis was performed using the same nonlinear mixed model, to which a bin factor was added. This resulted in a 2 (congruence) * 2 (group) * 7 (bin) design. A distinct analysis was performed on the first bin of CAF since accuracy for the fastest responses is considered above all as the key variable to assess impulsive action selection while other bins have little importance on this aspect according to the activation-suppression model (van den Wildenberg et al., 2010). Concerning the delta plots, we compared the dynamics of selective inhibition between groups. To this end, we computed slope values, which are usually used as measure of the strength of selective inhibition. We compared the slope values using a linear mixed model with slope (position in RT distribution) and group as fixed effects, and participant as a random effect. This resulted in a 2 (group) * 6 (slope) design. Since the activation-suppression model postulates that the last slope of the delta plots allows the assessment of the strength of the selective inhibition mechanism, we conducted a distinct analysis on this last slope (Ridderinkhof, 2002). All *p* values for linear mixed models were computed using the anova function that uses *F* tests, while *p* values for nonlinear mixed models were computed with the Anova function that calculates Wald chi-square tests (Anova {car}). Post hoc Tukey tests were used for further analyses when significant effects were found. The adjusted *p* values were obtained with the Tukey glht function from the multcomp package, which uses individual *z* tests instead of t-test when mixed models are used (Hothorn et al., 2007). Finally, we conducted correlation analyses

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between the measures of impulsive response selection (accuracy for the first bin of the incongruent CAF), suppression (steepness of the last delta-plot slope) and the BIS-10 scores with Spearman's rank correlation tests. For all our analyses, we used a significance threshold of $p = 0.05$.

3. Results

3.1. Group effects on overall congruence effect

Patients with PD responded faster than HC, irrespective of the congruence of the situation, as revealed by a significant group effect on RTs, $F(1, 31) = 5.07$, $p = 0.03$. The classic congruence effect was observed, with longer RTs in the incongruent versus congruent situation, $F(1, 14382) = 624.9$, $p < 0.0001$. Thus, all participants were slower overall when the relevant and irrelevant dimensions of the stimulus dictated conflicting responses. However, although both groups were affected by conflict situations, the congruence effect was greater in the patients with PD (74.4 ms) than in HC (34.6 ms; Fig. 2A). This was confirmed by a significant interaction between group and congruence, $F(1, 14382) = 79.1$, $p < 0.0001$. This difference arose because the patients were faster than HC in the congruent situation ($z = -3.06$, $p = 0.008$), whereas they had similar RTs in the incongruent situation ($z = -1.1$, $p = 0.6$). Concerning accuracy, patients made more errors overall than HC ($\chi^2 = 12.4$, $p = 0.0004$). We also observed a congruence effect on accuracy, with more errors in the incongruent versus congruent situation ($\chi^2 = 1303.8$, $p < 0.0001$). The size of the congruence effect on accuracy also differed between groups ($\chi^2 = 53.8$, $p < 0.0001$). Patients made more errors than HC in the incongruent situation (39.1 vs 21.3; $z = -4.3$, $p < 0.0001$), whereas both groups displayed similar accuracy in congruent situations (9.2 vs 7.3; $z = -1.3$, $p = 0.5$).

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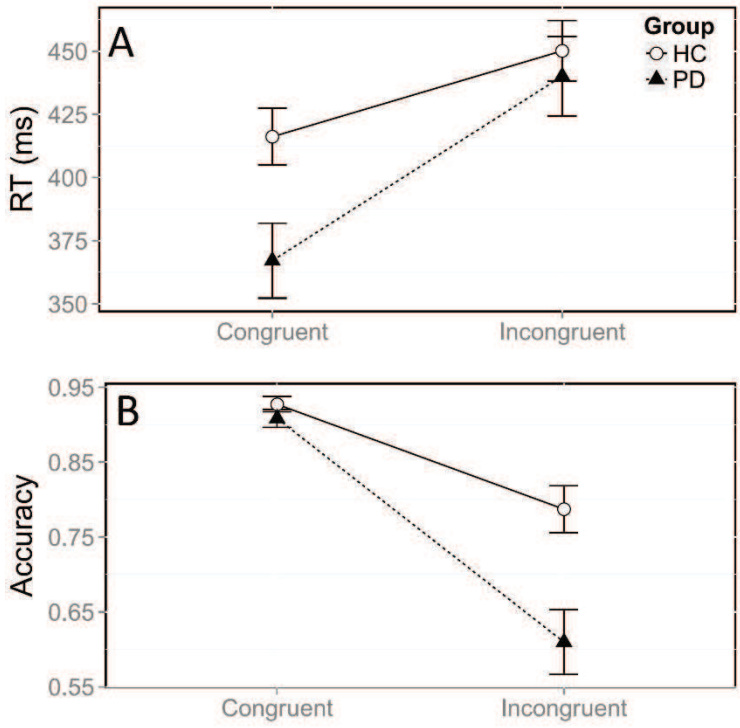


Figure 2: Mean RT (A) and accuracy (B) according to congruence and group. Error bars represent the standard error of the mean.

3.2. Group effects on impulsive response selection

To assess group differences in impulsive response activation dynamics, we analyzed the data with CAFs, which showed accuracy as a function of the RT distribution divided into seven bins. Figure 3 shows the CAFs of HC and patients for the incongruent (Fig. 3A) and congruent (Fig. 3B) situations. Congruence had a strong overall impact on accuracy (χ^2 = 1103.9, $p < 0.0001$). However, the extent of this congruence effect differed between groups, with a greater effect in patients than in HC (χ^2 = 11.9, p = 0.0005). Importantly, the congruence effect depended strongly on the time taken to respond. Faster RTs were associated with more fast errors in the incongruent situation, as revealed by a significant interaction between congruence and bin (χ^2 = 537.6, $p < 0.0001$). The overall dynamics of the congruence effect did not change between groups, as the interaction between congruence, bin and group failed to reach significance (χ^2 = 9.5, p = 0.14). However, the variance associated with the

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other bins is likely to mask this effect (Wylie et al., 2009b). Furthermore, impulsive action selection is best portrayed by the first bin of CAF according to the activation-suppression model. Accordingly we conducted a distinct analysis focusing on the first bin. The congruence effect was far stronger in patients that in HC, owing to a higher proportion of fast errors in the PD group (78.6% in PD vs. 54.1 % in HC; $\chi^2 = 31.4$, $p < 0.0001$). This was confirmed by post hoc tests revealing that patients and HC were equally accurate in the congruent situation ($z = 0.6$, $p = 0.9$), but differed strongly in the incongruent situation ($z = -5.1$, $p < 0.0001$). Furthermore, Figure 3 suggests that the patients' first bin represented shorter RTs than the HC bin did. This was confirmed by the significant difference in RTs for the first bin between the PD and HC groups, $F(1, 31) = 15.5$, $p < 0.0001$. These results mean that the patients with PD responded faster and displayed greater impulsive action selection elicited by the irrelevant stimulus dimension than HC.

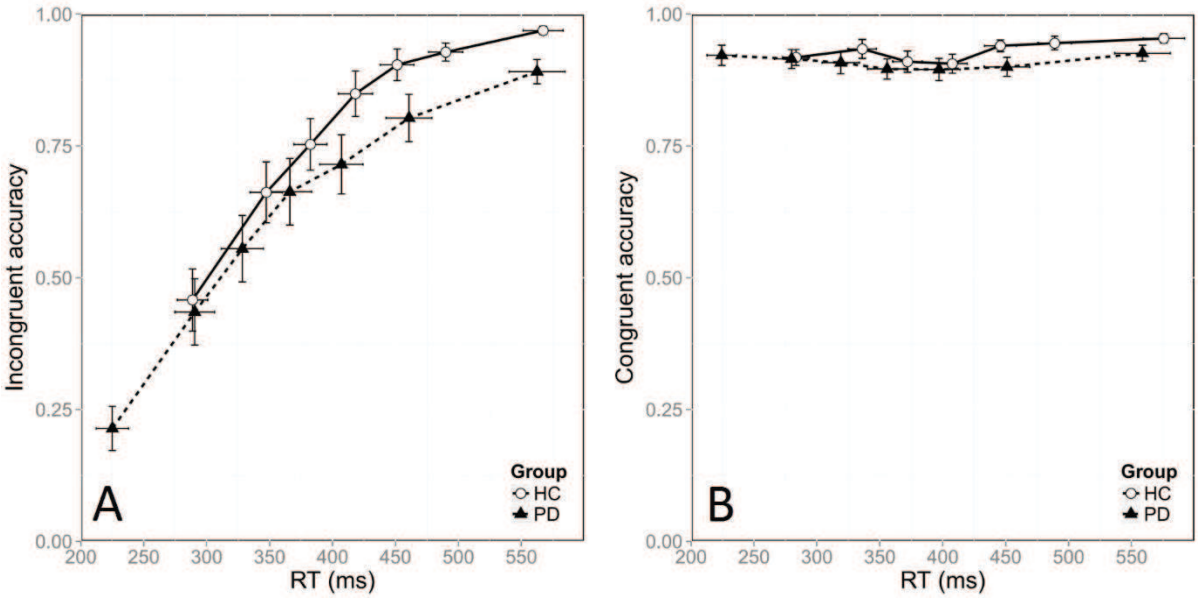


Figure 3: CAFs for the incongruent (A) and congruent (B) situations, plotted against RT distribution, as a function of group. Error bars represent the standard error of the mean.

3.3. Group effects on selective inhibition

We used delta plots to assess the strength of selective inhibition. According to the activation-suppression model, the slopes between the bins of the congruence effect best reflect

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the strength of this process. Figure 4 shows the typical decreasing delta plots for both patients and HC. Our analyses first revealed that the slopes were more negative for the slowest segments of the RT distribution, $F(1, 318) = 6.7$, $p = 0.01$. Faster RTs were associated with slopes that were less steep, indicating that selective inhibition was not as effective as it was for slower responses. The overall slope of the congruence effect was the same for both groups, indicating that selective inhibition was similar for both HC and patients, $F(1, 31) = 0.46$, $p = 0.5$. We focused our final analysis on the last segment of the delta plots, which is the most informative when it comes to the strength of selective inhibition. This analysis confirmed that selective inhibition was similar for both patients and HC, with no difference in the steepness of the last slope, $F(1, 31) = 0.5$, $p = 0.48$.

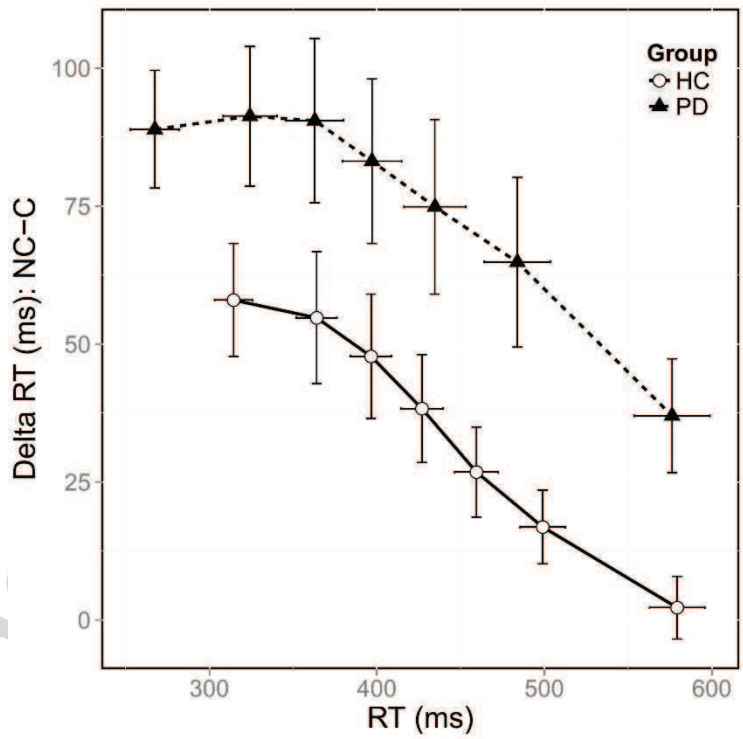
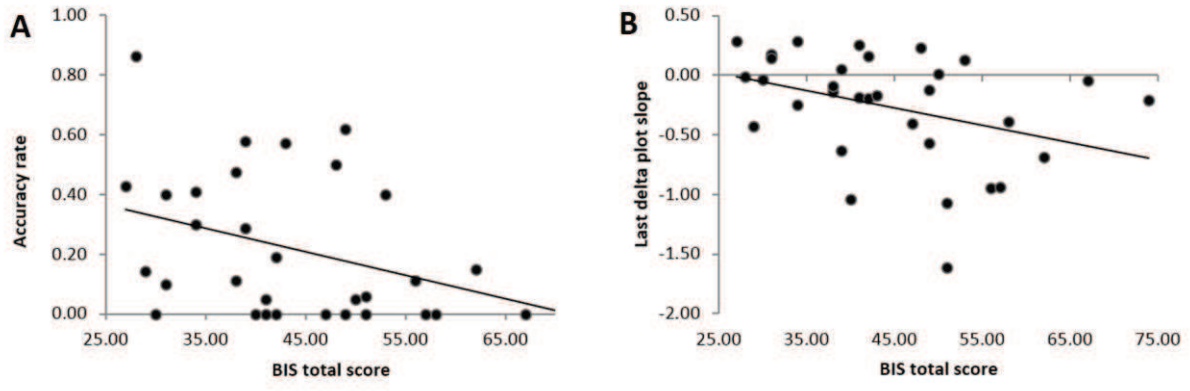


Figure 4: Delta plots showing changes in the congruence effect (incongruent [NC] RT - congruent [C] RT) as a function of RT distribution for HC and patients with PD. Error bars represent the standard error of the mean.

3.4. Relationship between trait impulsivity and impulsive action selection and suppression

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We did not find any correlation among HC between the BIS-10 scores and either the accuracy of the first CAF bin for the incongruent situation, or the steepness of the last delta-plot slope (all *p*s > 0.05). Among the patients, however, we found a negative correlation between accuracy for the first CAF bin in the incongruent situation and both the BIS-10 total score (r = - 0.38, p = 0.03) and its cognitive (r = - 0.37, p = 0.03) and motor (r = - 0.38, p = 0.03) subscores. In other words, greater impulsivity, as assessed by the questionnaire, was associated with greater impulsive action selection in the task. Furthermore, the last delta-plot slope was negatively correlated with the BIS-10 total score (r = - 0.36, p = 0.04) and cognitive subscore (r = - 0.36, p = 0.04), meaning that higher scores on the questionnaire were accompanied by steeper last slopes of the delta plot. To ensure the absence of influential outliers, we checked Cook's distance and found no values above 0.5 (values below 1 being considered of little influence on the correlation; Cook et al., 1982). We also found a positive correlation between accuracy in the first bin of CAF and the last delta-plot slope value in patients (r = 0.37, p = 0.03), meaning that higher accuracy in the first bin of CAF was associated with higher slope values, and thus, with weaker selective inhibition. As a whole, higher scores on the BIS-10 were associated with stronger impulsive action selection, but also with stronger late selective inhibition (Fig. 5). It should be noted that the patients with PD did not differ from HC on the BIS-10 scores (t = - 0.38, p = 0.7).



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Figure 5: Scatterplots depicting (A) the negative correlation between the BIS total score and the accuracy rate for the first CAF bin (r = -0.38) and (B) the negative correlation between the BIS total score and the last delta-plot slope value (r = -0.36) among patients with PD.

3.5. Relationship with PD clinical features

We also investigated whether clinical features of PD were related to the measures of cognitive action control and its dynamics. To this end, we tested whether the overall congruence effect, the accuracy in the first bin of CAF and the last slope of the delta-plots were related to disease duration, disease severity (UPDRS motor score and Hoehn & Yahr ratings) and levodopa equivalent daily dose. We found no significant relationship between those task results and disease characteristics (all $p > 0.10$)."

4. Discussion

The purpose of this study was to investigate the impact of PD on cognitive action control and to specify the potential link between behavioral measures of impulsive action selection and suppression and trait impulsivity in both HC and patients. To this end, we used an oculomotor version of the Simon task (Duprez et al., 2016) and analyzed the results according to the activation-suppression model (Ridderinkhof, 2002). The use of distributional analyses as per this model allowed us to investigate impulsive action selection and suppression, both of which are regarded as core mechanisms of cognitive action control. We also used correlation analyses to investigate the specific link between the measures of these two mechanisms and self-reported impulsivity, as assessed by the BIS-10. Our main prediction was that patients with PD would display more impulsive action selection than HC, and less proficient engagement of the selective inhibition mechanism. We further expected measures of impulsive action selection and suppression to be associated with BIS-10 impulsivity scores in both HC and PD.

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We found the typical congruence effect on RT and accuracy, showing that conflict situations generate longer RTs and more errors. This effect was greater in patients with PD than HC, meaning that patients experienced greater difficulty resolving conflict situations. Greater congruence effects in patients have already been reported in several studies, whether or not the patients were on medication (Praamstra et al., 1999, 1998; van Wouwe et al., 2016, 2014; Wylie et al., 2009a, 2005). Importantly, the greater congruence effect observed in our study was due not to slowing in the incongruent situation, but rather to the fact that patients were faster than HC in the congruent situation, as already reported by Praamstra et al. (1999). The reason why we did not observe faster responses by patients than by HC in the incongruent situation is because the congruence effect is based on correct responses. Most of the incorrect responses provided by patients in the incongruent situation had very fast RTs, as we discuss below. Thus, most of the responses in which patients were faster than HC in the incongruent situation did not appear in the analysis of the congruence effect because most of them were erroneous.

A number of studies investigating the impact of PD on impulsive action selection have used distributional analyses, in accordance with the activation-suppression model (Ridderinkhof, 2002). Most of these studies assessed impulsive action selection and suppression in medicated PD patients. While some of them have demonstrated higher automatic activation in PD (Wylie et al., 2009a), which may be restricted to patients with the most severe motor symptoms (Vandenbossche et al., 2012; Wylie et al., 2010a), while others have found no effect of PD on CAFs (van Wouwe et al., 2014). Another study which investigated the dynamics of cognitive action control in patients with and without their medication found no difference between PD patients and HC on impulsive action selection, whatever the patients were assessed with or without medication (van Wouwe et al., 2016). In the current study, the fact that patients made more fast errors in the incongruent situation than

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HC did argues in favor of stronger impulsive action selection in PD, as the rate of fast errors is regarded as the main indicator of susceptibility to impulsive action selection (van den Wildenberg et al., 2010). Importantly, the responses of patients and HC in the first bin were equally accurate in the congruent situation, thus ruling out an attentional bias in patients. Moreover, patients were faster than HC in both the congruent and incongruent situations. Thus, the increase in response speed in PD is probably the main explanation for the patients' dramatic decrease in accuracy in the incongruent situation. According to the activation-suppression model, the selective inhibition of erroneous responses is only effective when responses are delayed. Thus, responding faster increases the risk of errors. In addition, we observed that slower responses in PD were associated with accuracy similar to that of HC, supporting the notion that responding faster generates more errors.

As a whole, we found that patients' conflict resolution was impaired, and this impairment originated from greater impulsive action selection. The strength of selective inhibition seemed unaffected. We measured faster responses and a greater number of fast errors in PD patients compared to HC. Faster oculomotor reactions in PD patients have also been observed in another study using an oculomotor Simon task (Fielding et al., 2005). Faster responses would be expected by a speed-accuracy tradeoff biased toward speed. However, in an oculomotor Simon task, Fielding et al. (2005) strongly biased instructions toward accuracy and observed that PD patients were faster than healthy controls. They explained this enhanced speed in PD by the dysfunction of an inhibitory mechanism usually suppressing direct stimulus-driven response. Furthermore, while volitional saccadic eye-movements are altered in both RT and accuracy in PD, visually-guided saccades seem unaffected or even faster (Briand et al., 1999; Terao et al., 2013). For example, Briand et al. (2001) also found that patients were faster than HC in a reflexive visual-orienting task. The authors explained this finding by surmising that patients with PD have hyper-reflexive orienting of spatial attention. Their explanation was

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based on the assumption that eye movements are controlled by two separate attentional systems: a voluntary one that is responsible for volitional eye movements and which inhibits more reflexive one that controls visually guided saccades. According to the authors, PD primarily disrupts the voluntary system, which involves the basal ganglia, freeing the reflexive system from inhibition and thus facilitating reflexive eye movements. These interpretations are in line with the explanation by Terao et al. (2013) who proposed that such faster responses could result from disinhibition of the superior colliculus secondarily to impairment of the prefrontal-basal ganglia networks in PD, and/or from overactivity in the parietal cortex that would compensate for the motor disorders. This view fits in well with the general assumption of dual-route models whereby stimulus processing in a conflict situation follows two parallel routes (a mainly automatic one and a controlled one) that converge to activate a response (Kornblum et al., 1990). Thus, the greater congruence effect in our patients with PD may have resulted from hyper-reflexive orientation of attention.

Cognitive action control is thought to rely on prefrontal-basal ganglia circuits involve the pre-SMA, IFC, and STN (Aron et al., 2007; Forstmann et al., 2008a, 2008b; Spieser et al., 2015). Forstmann et al. (2008) used a Simon task coupled with fMRI to investigate the structures associated with the dynamics of response activation and suppression. They showed that higher impulsive action selection (portrayed by the first CAF bin) is associated with greater activity in the pre-SMA, while stronger selective inhibition (portrayed by the last delta-plot slope) is associated with greater activity in the IFC. Recent evidence from a study using transcranial direct current stimulation further confirms the role of the pre-SMA in the expression of impulsive actions (Spieser et al., 2015), while the IFC has repeatedly been reported to be an important structure for inhibitory control (Aron et al., 2004). Thus, higher impulsive action selection, as assessed by the number of fast errors in CAFs, is usually associated with activation of the pre-SMA in manual versions of the task (Forstmann et al.,

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2008a). Switching to an oculomotor response modality engages additional areas, such as the frontal and parietal eye fields, which are thought to be involved in volitional and reflexive eye movements, respectively (Gaymard, 2012). Since these cortical areas are linked to the basal ganglia, and since PD disrupts prefrontal-basal ganglia circuits (Watanabe and Munoz, 2011), an imbalance between the automatic and controlled systems might well occur, leading to a bias toward automatic activation. This would explain why patients made more fast errors in our study. An alternative explanation is that patients with PD have a different speed-accuracy trade-off strategy from controls. They may thus have focused their performance on speed rather than on balancing speed and accuracy, as instructed. However, focusing on speed would also induce greater selective inhibition difficulty, reflected in a less negative last delta-plot slope (Wylie et al., 2009a).

Still according to the activation-suppression model (Ridderinkhof, 2002), a steeper negative last delta-plot slope is usually interpreted as reflecting stronger selective inhibition (see van den Wildenberg et al., 2010, for a review). We also observed the classic Simon task's delta-plot pattern, with a decreasing congruence effect across RT distribution. This pattern was similar for both patients and HC, and a specific analysis of the last slope failed to reveal any group differences. This suggests that patients displayed asimilar inhibition of impulsive action selection to HC. This contrasts with previous studies, except for one recent one (van Wouwe et al., 2016). Most studies have shown a deficit in selective inhibition in PD, revealed by a less negative last delta-plot slope (van Wouwe et al., 2014; Wylie et al., 2009a; Wylie et al., 2010a). This finding of selective inhibition difficulty is consistent with studies that have found impaired inhibition in patients with PD by assessing their performances on a stop task (Gauggel et al., 2004; Obeso et al., 2011).

One possible explanation for the discrepancy between the literature and our results is that the patients in our study were younger and their disease was less severe than in other studies

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(Wylie et al., 2010a, 2009a, 2009b). As disease severity and age (assessed in HC) have been reported to modulate cognitive action control and the dynamics of activation and suppression (Castel et al., 2007; Duprez et al., submitted; Juncos-Rabadán et al., 2008; Wylie et al., 2010a), these factors could account for some of the differences between our results and the literature. Another possible explanation is that the lack of difference in the delta plots could stem from the fact that we used an oculomotor response mode. The last delta-plot slope in most of the studies investigating PD with the Simon task covered RTs lasting 600-700 ms, whereas in ours, it covered RTs of 500-600 ms (van Wouwe et al., 2016, 2014; Wylie et al., 2010a, 2009a, 2009b). Our version of the task may therefore have generated responses that were too fast for the selective inhibition mechanism to be as fully engaged as it is in manual Simon tasks.

Our results did not reveal any relationship between task measures and dopaminergic medication dosage. Similarly, in a recent study comparing PD patients with and without dopaminergic medication, van Wouwe et al. (2016) did not observe any correlation between treatment dosage and task results. These authors reported a positive effect of the treatment on selective inhibition but no effect on impulsive action selection and the patients with treatment were no more different that HC. This could explain why our medicated patients were not different from HC in late selective inhibition. However, both studies do not firmly rule out a potential role of dopamine, at least in selective inhibition and further studies are needed to clarify the role of dopaminergic therapy on cognitive action control.

The second purpose of the current study was to assess the link between impulsive action selection, suppression, and trait impulsivity, as assessed by the BIS-10 questionnaire, in both HC and patients with PD. Recent studies of HC have yielded mixed results concerning the overlap between different measures of impulsivity. Cyders and Coskunpinar, (2012) who used several tasks, including the Go/No-Go task, failed to find a link between the experimental

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measures and the UPPS-P impulsive behavior scale (a self-report questionnaire). By contrast, other studies have found that higher self-reported impulsivity is linked to higher error rates in Go/No-Go or antisaccade tasks (Aichert et al., 2012; Reynolds et al., 2006). Nombela et al. (2014) showed that, in patients with PD, BIS scores and behavioral measures yielded by a No-Go saccade paradigm or a Stroop task were part of the same factor explaining most of the variance in a principal components analysis. Furthermore, there is some electrophysiological evidence to suggest that scores on impulsivity questionnaires are related to inhibition abilities. When Shen et al. (2014) recorded event-related potentials during a stop task, they found that higher scores on an impulsivity questionnaire were associated with lower amplitudes of the P3 component known to be associated with successful inhibition. We hypothesized that distributional analyses are a more powerful tool for capturing this potential link, as they provide access to the fastest responses. In our patients, the highest BIS impulsivity scores were associated with the lowest accuracy. Accuracy for the first bin of the incongruent situation was correlated with both the BIS-10 total score and cognitive and motor subscores (reflecting the tendencies to making quick cognitive decisions and to act without thinking; Patton et al., 1995). This means that those patients who were more prone to act without thinking or to make quick decisions were the ones who displayed the most impulsive action selection in the Simon task. Furthermore, we found a negative correlation between both the BIS-10 total score and cognitive subscore and the steepness of the last delta-plot slope. Taken together, our results suggest that the patients who rated their impulsivity higher on the BIS-10 questionnaire were those who displayed the greatest impulsive action selection, as well as the strongest late selective inhibition. The fact that impulsivity revealed by the BIS scale was associated with both increased impulsivity and increased response suppression in the Simon task seems counterintuitive. One possible explanation could rely on the central role of the STN in these processes. Indeed, the STN has been involved in trait impulsivity (Hälbig et al.,

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2009, Houvenaghel et al., 2016) as well as in both selection and suppression of impulsive responses (Wylie et al., 2010). It is thus possible that the impairment of the frontal-subthalamic network in PD might be reflected in both the assessment of trait impulsivity and different aspects of the experimental evaluation of action control. Beyond a common neural substrate for both increased impulsivity and increased response suppression, the concurrent correlations with the BIS score could be explained by the temporal dissociation between these two mechanisms (Wylie et al., 2010).

We found no difference in BIS-10 scores between patients and HC, in contrast to other studies where patients with PD rated it more highly than HC did (Isaias et al., 2008; Nombela et al., 2014). However, the patients in these studies were older than ours, and their disease was more severe, which could explain the lack of difference we observed. While PD patients and HC were similar regarding BIS scores, strong differences appeared in the results of the Simon task, especially for impulsive action selection. These measures assess impulsivity differently: the Simon task gives information on impulsive action selection and suppression while the BIS assesses impulsivity in a broader manner, as a personality trait. Our results suggest that impulsive action selection, measured by the Simon task, could not be detected by such a questionnaire, which does not specifically evaluates this process. Conversely, such an experimental task does not evaluate impulsivity as a personality trait. However, the correlation between the BIS scores and the results of the experimental task supported the existence of a link between these two measures of impulsivity, which had already been suggested by other authors (Nombela et al., 2014). The activation-suppression model allowed us to study the dynamics of cognitive action control and proved useful in exposing this link. However, our results do not go any way toward explaining its nature. We can only speculate that a common cause resulting from the disease influenced both our measures. Inferences on the neural mechanisms explaining this link or its impact on the performances of the patients

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cannot be based only on a correlation. However, this result could have interesting clinical implications. Nombela et al. (2014) have reported that BIS scores and task measures, in a Stroop task or a saccadic Go/No-Go task, were part of a same modality of impulsivity in PD patients. They further showed that this mode was correlated to a dementia rating scale. Considering that our patients were similar to HC on BIS scores but very different at the task, one may wonder whether impulsivity related to prefronto-basal ganglia dysfunction could be first apparent in experimental measures, before its clinical expression and detection by neuropsychological tests. Experimental conflict tasks could thus help in early detection of impulsive behaviors or cognitive decline. Though highly speculative, this hypothesis could be the base for further studies investigating the links between the different types of impulsivity and their clinical implications. Considering the complexity of impulsivity, especially in PD (Robert et al., 2009), it would be relevant to assess impulsive action selection and suppression, as well as other measures of impulsivity, in PD patients with impulse control disorders and to perform longitudinal studies in PD using multiple measures of impulsivity.

5. Conclusion

The effect of PD on cognitive action control has been described in several studies, and in recent years, the activation-suppression model has increasingly been used to investigate the processes of impulsive selection and suppression more thoroughly. Two major results emerged from the current study. First, the combined use of an oculomotor version of the Simon task and the activation-suppression model allowed us to show that patients with PD display greater impulsive action selection, probably as the result of faster responding due to hyper-reflexive orientation of spatial attention. This hypothesis could be confirmed by directly comparing patients' performances on manual and oculomotor versions of the task. Second, we found a correlation between an experimental impulsivity marker and a clinical scale measuring trait impulsivity. Our investigation of the dynamics of cognitive action

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control according to the activation-suppression model suggested that these measures share common features. However, this could be specific to our oculomotor version of the task. It would therefore be useful to check whether this link can also be found when manual versions of the task are combined with the activation-suppression model. Furthermore, the nature of this relationship needs further clarification, and more studies are needed, featuring specific impulsivity scales such as the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease (Weintraub et al., 2012). This would greatly help to characterize the patients and the severity of their impulsivity symptoms. It is crucial to conduct these investigations, as the impulsivity that arises from PD and/or its treatment can have a dramatic social impact.

Relevant conflicts of interest / financial disclosures:

Nothing to report

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Highlights

- We compared action selection and suppression between PD patients and controls
- We investigated the link between behavioral and trait impulsivity
- PD patients displayed a higher impulsive action selection than controls
- Impulsive action selection and suppression were correlated with trait impulsivity

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