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Conflict of interest statement

Dr Sophie Drapier received speech honorarium from Teva and Medtronic and served on scientific advisory boards for Aguettant and Britannia.

Dr Marc Vérin has served on the Scientific Advisory Board for Aguettant and Orkyn and received speech honorarium from Teva and Medtronic.

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

Abstract

Introduction: Continuous subcutaneous apomorphine infusion (CSAI) is increasingly used in Parkinson's disease (PD), notably in patients contraindicated for subthalamic deep brain stimulation. Although it has been suggested that CSAI is safe regarding cognition, few studies have actually investigated its effect, especially on cognitive control which is a crucial process for goal-directed behavior. More specifically, its impact on the dynamics of cognitive action control, as reflected by the activation and suppression of impulsive responses, has yet to be investigated, which is the objective of the present study.

Methods: We compared cognitive action control between baseline (M0) and 6 months (M6) after the start of add-on CSAI by administering an oculomotor Simon task to 20 patients with mild to moderate PD. We used the activation-suppression model to determine whether CSAI had an effect on either the impulsive errors made in conflict situations or the suppression of these responses.

Results: We found no difference between M0 and M6 in the congruence effect regarding either reaction time or accuracy, indicating that overall conflict resolution was not influenced by CSAI. Furthermore, the rate of fast errors in the conflict situation and the last slope of the delta plots (reflecting the strength of impulsive response suppression) were unaffected by the treatment. The 95% confidence intervals calculated for the treatment effect on both of these measures fell below the range of usual meaningful effects.

Conclusion: We found no difference between M0 and M6, which strongly suggests that CSAI does not impair the dynamics of cognitive action control.

1. Introduction

Patients with Parkinson's disease (PD) whose motor fluctuations can no longer be satisfactorily controlled by oral medication can be proposed continuous subcutaneous apomorphine infusion (CSAI). This treatment has repeatedly been reported to have a beneficial effect, with reductions in motor fluctuations, as well as in nonmotor symptoms [1]. By contrast with previous reports [2], recent studies have suggested that the beneficial motor effect of CSAI comes without the deleterious cognitive side effects associated with other treatments such as deep brain stimulation of the subthalamic nucleus [3, 4, 5]. So far, however, few studies have examined the effect of CSAI on the cognitive functions thought to be affected by other antiparkinsonian treatments.

One of the most important of these functions is cognitive control, as it allows us to adapt to our environment according to our intentions, ignoring any irrelevant information [6]. Among the different processes participating in an efficient cognitive control, cognitive action control refers to the online control allowing to suppress unwanted and automatic action tendencies in favor of an intention-driven behavior [6]. This cognitive process is often assessed using experimental conflict tasks such as the Simon task [7]. This task requires participants to produce a "left" or "right" answer according to the color of a stimulus displayed on the left- or righthand side of a screen, regardless of its position. When the position and color of the stimulus are incongruent and indicate different responses, a conflict arises and the participant has to suppress the automatic response activated by the position of the stimulus. Incongruent situations lead to more errors, and responding accurately has a cognitive cost expressed as an increase in reaction time (RT). This is commonly called the congruence effect.

During the past decade, most studies investigating cognitive action control have focused on its dynamics, using the activation-suppression model and distributional analyses [8]. This model postulates that fast responses in incongruent situations are more error-prone, reflecting a process called *impulsive action selection*, while slow responses indicate a smaller congruence effect, reflecting the efficacy of a suppression mechanism. The *conditional accuracy function* (CAF) can be used to investigate impulsive action selection, as it represents accuracy as a function of congruence plotted against RT distribution, divided into several bins (usually 5-7). Lower accuracy for the first incongruent bin indicates stronger impulsive action selection. The suppression mechanism is shown by the delta plot representing the congruence effect (incongruent RT minus congruent RT for correct responses) as a function of RT distribution, as with the CAF. The steeper the negative slope between the two last bins, the greater the suppression (see [9] for a review).

The effect of PD and its treatment on these dynamics has been thoroughly studied in recent years. For instance, patients with PD have been shown to display stronger impulsive action selection and weaker suppression, compared with healthy controls [10, 11, 12]. Antiparkinsonian treatment also has an effect on these dynamics, as van Wouwe et al. [13] found that patients with PD displayed greater suppression when they were on their dopaminergic medication than when they were off medication. Furthermore, a study by Wylie et al. [14] revealed that dopamine agonists weaken the suppression of irrelevant activations, while the number of impulsive errors is unaffected. In this study, the dopamine agonist dose was correlated with the strength of suppression, with higher doses being associated with weaker suppression. Deep brain stimulation of the subthalamic nucleus impacts both impulsive action selection and suppression. Wylie et al. [15], for example, showed that patients undergoing active stimulation make more impulsive errors than when they are off stimulation, but are more efficient at suppressing irrelevant activations, providing they take enough time to respond.

Although some studies have suggested that CSAI has no deleterious cognitive effects, its potential effect on impulsive action selection and suppression in conflict situations has never been examined. CSAI does not seem to modify performances in standard neuropsychological assessments performed during routine clinical care [3, 4, 5, 16], but an effect on the dynamics of cognitive action control cannot be ruled out. Although the impact of classic oral agonists has already been studied [14], apomorphine differs from these dopaminergic agonists in terms of its pharmacodynamics and continuous administration modality [17]. The goal of the present study was to verify that add-on CSAI has no negative impact on cognitive action control and its dynamics. To this end, we used an oculomotor version of the Simon task that has proved to reveal subtle changes in cognitive action control in PD or healthy older participants [18, 10]. We compared the classic congruence effect, as well as the key features of impulsive action selection and suppression, measured before the introduction of CSAI and six months later in patients with mild to moderate PD.

2. Methods

Table 1: Clinical data (mean ± standard deviation) before (baseline) and after (M6) the start of CSAI. Statistical comparisons were carried out using the Wilcoxon paired test. Dyskinesia and fluctuation scores were calculated as the sum of items 32 to 35 and 36 to 39 (respectively) of the part IV of the UPDRS.

	N	Baseline	M6	p-value	V statistic
Sample size		20	20		
Age (years)	20/20	58.9 ± 10.5	-		
Education (years)	20/20	19.2 ± 8.7	-		
Sex (M:F)	20/20	9:11	-		
Disease duration	20/20	11.7 ± 4.8	-		

Hoehn and Yahr rating-ON	18/20	1,1 ± 1	0.8 ± 0.8	0.32	V=37.5
Hoehn and Yahr rating-OFF	18/20	2.1 ± 0.8	2.1 ± 0.6	0.65	V=27.5
Schwab & England rating - ON	18/20	91.7 ± 7.1	92.3 ± 9	0.86	V=12.5
Schwab & England rating - OFF	18/20	71.1 ± 16	75.9 ± 17	0.5	V=48
UPDRS II On med	20/20	4.4 ± 3.2	4.8 ± 3.1	0.98	V=67
UPDRS II Off med	20/20	15.5 ± 4.7	13.7 ± 6	0.3	V=96.5
UPDRS III On med	20/20	13.2 ± 9.2	13 ± 8.2	0.9	V=66.5
UPDRS III Off med	19/20	35.3 ± 12.19	36.7 ± 10	0.5	V=48
UPDRS IV	18/20	6.1 ± 2.2	5.1 ± 2.3	0.2	V=73
Dyskinesia score (Items 32-35)	18/20	2.1 ± 1.5	2.1 ± 1.6	0.7	V=50.5
Fluctuation score (Items 36-39)	18/20	**3.2 ± 1.2**	**2.1 ± 1.1**	**0.02**	V=59
LEDD total (mg/day)	20/20	**1089.2 ± 265.2**	**1499.8 ± 343.7**	**0.001**	V=13
Levodopa	20/20	**837.6 ± 288.5**	**479.4 ± 226.6**	**0.001**	V=145
Agonist	20/20	245 ± 125.6	195.3 ± 121	0.05	V=64
Apomorphine	20/20	-	826.9 ± 207.5		
LEDD total oral med (mg/day)	20/20	**1082.6 ± 252.3**	**674.7 ± 244.5**	**0.0005**	V=150
MDRS	20/20	138 ± 4.5	137.7 ± 5.2	0.7	V=75.5

1 Note. UPDRS = Unified Parkinson's Disease Rating Scale; LEDD = levodopa equivalent daily dose; MDRS = Mattis

2 Dementia Rating Scale

3 2.1. Patients

4 We recruited 20 patients with idiopathic PD from the Neurology Department of Rennes University Hospital (France)

5 for inclusion in this study (Table 1). They had mild to moderate disease severity (Hoehn and Yahr stages I-III in the on-

6 medication state [19]) and had been hospitalized in order to introduce apomorphine hydrochloride treatment

7 (Apokinon®; Aguettant, Lyon, France) using an infusion pump (Microjet Crono PAR; Cane Medical Technology, Italy)

8 as part of their routine clinical care. The CSAI treatment had been proposed to these patients due to motor fluctuations

9 occurring despite an optimized oral treatment. Before CSAI, these patients displayed an averaged fluctuation score

10 (calculated as the sum of items 36 to 39 of the UPDRS IV) of 3.2 ± 1.2 and an average off-state score of 1.15 ± 0.5.

11 This score represents a proportion of 26 to 50 % of off-state during the day. CSAI has been reported to reduce these off-

12 state periods known to have a strong negative impact on patients' daily life [20, 21]. Patients were free of severe

13 cognitive deterioration (Mattis Dementia Rating Scale score > 130; [22]), and had no other neurological or psychiatric

14 pathologies. The severity of their motor symptoms was assessed using the third part of the Unified Parkinson's Disease

15 Rating Scale (UPDRS). All patients were assessed under their usual medication at baseline (before the introduction of

16 CSAI) and after 6 months of apomorphine treatment (M6; mean time since baseline: 6 ± 0.3 months). At baseline,

17 medication included both dopamine agonists and levodopa therapy in 19 patients, and levodopa alone in one patient.

18 The study was approved by the ethics committee of Rennes University Hospital and conducted in accordance with the

19 Declaration of Helsinki and current French legislation (Huriet Act). All the patients gave their informed consent to take

20 part in the study.

21

22 2.2. CSAI treatment

23

CSAI was used during the day for a mean duration of 13.6 ± 4 hours (range: 6-20) at a mean hourly rate of 4.9 ± 0.8 mg (range: 3.8–7) and a mean bolus number of 2.6 ± 1.5 per day (range: 0-5) with a mean dose of 3.4 ± 1.3 mg (range: 0–5) per bolus.

2.3. Task design and procedure

We used an oculomotor version of the Simon task in which participants were instructed to make a left or right eye movement according to the color (blue or yellow) of a stimulus, while ignoring its location (left or right), as fast and accurately as possible. Participants performed a total of 300 trials, divided into five blocks with self-paced breaks between these blocks. Two types of situation happened pseudorandomly with an equal probability: a congruent one where the location of the stimulus corresponded to the response side indicated by its color; and an incongruent one where the location and color of the stimulus indicated opposite responses. Color mapping was pseudorandomly assigned to each patient, and the reverse mapping was used at M6. Eye movements were recorded using an EyeBrain T2® head-mounted eyetracker (e(ye)BRAIN, Ivry-sur-Seine, France) with a 300 Hz sampling rate and an angular resolution of 0.5°. For more details, see [18].

2.4. Analysis

All data analyses were performed using R© software (Version 3.1.0). The first eye movement after stimulus presentation was deemed to be the participant's response, and was considered correct if it corresponded to the side indicated by the color of the stimulus. Eye movements with an amplitude below 2° and a latency below 100 ms or above 1000 ms were removed (for more details, see [18]). Outlier latencies of more than three standard deviations from mean RT were also discarded. Overall, 2.03% of the data were removed. For each participant, we calculated the mean RT for correct trials and mean accuracy for each congruence condition, to evaluate the congruence effect. We also used distributional analyses to assess impulsive action selection and suppression [8]. We computed CAFs and delta plots showing accuracy and the congruence effect (incongruent RT minus congruent RT of correct trials) as a function of RT distribution divided into five bins (see [18]). The first bin of each CAF in the incongruent situation was used to assess impulsive action selection, and the value of the final slope of each delta plot was used to assess suppression [9].

As accuracy was not normally distributed, it was arcsine transformed prior to the statistical analysis. The congruence effect, accuracy for the first bin of the incongruent CAF, and last slope value of the delta plot were compared between baseline and M6 using repeated-measures analyses of variance (ANOVAs). For each test, we checked the assumptions

of normality and homoscedasticity of the residuals. Clinical variables were compared using paired Wilcoxon signed-rank tests. The significance threshold was set at $p = 0.05$.

3. Results

3.1. Clinical effect of CSAI

We found a significant decrease in motor fluctuations, as assessed with the sum of Items 36-39 of the UPDRS-IV at M6, compared with baseline (Table 1; V = 59, $p = 0.02$). Oral treatment was significantly reduced at M6, with a significant decrease in the levodopa equivalent daily dose (LEDD; V = 145, $p = 0.001$), as well as in the total oral medication daily dose (V = 150, $p = 0.0005$). The oral agonist dose tended to decrease (V = 64, $p = 0.05$) whereas overall LEDD increased, owing to the introduction of apomorphine treatment (V = 13, $p = 0.001$).

3.2. Congruence effect

We found no difference between baseline and M6 in overall RT, suggesting that patients responded at the same speed before and after the introduction of CSAI ($F(1, 19) < 1$, $p = 0.4$). A strong congruence effect was found, with a significantly shorter RT in the congruent situation than in the incongruent one reflecting the cognitive cost of conflict resolution (Fig. 1; $F(1, 19) = 34.9$, $p < 0.0001$). No difference was found in the size of the congruence effect between baseline and M6, as revealed by the absence of a significant interaction effect (mean congruence effect = 89 ± 62 ms at baseline and 111 ± 72 ms at M6; $F(1, 18) < 1$, $p = 0.5$). This result suggests that the cost of conflict resolution was unaffected by the introduction of CSAI.

Overall accuracy did not differ between baseline and M6, suggesting that CSAI had no impact on patients' precision ($F(1, 19) < 1$, $p = 0.9$). As with RT, we found a strong congruence effect, with a significant decrease in accuracy in the incongruent situation, compared with the congruent one (Fig. 1; $F(1, 19) = 138.2$, $p < 0.0001$). The size of the congruence effect on accuracy was unaffected by CSAI, as suggested by the absence of a significant interaction effect (mean congruence effect = 39% ± 28 at baseline and 46% ± 28 at M6; $F(1, 18) = 1.4$, $p = 0.24$).

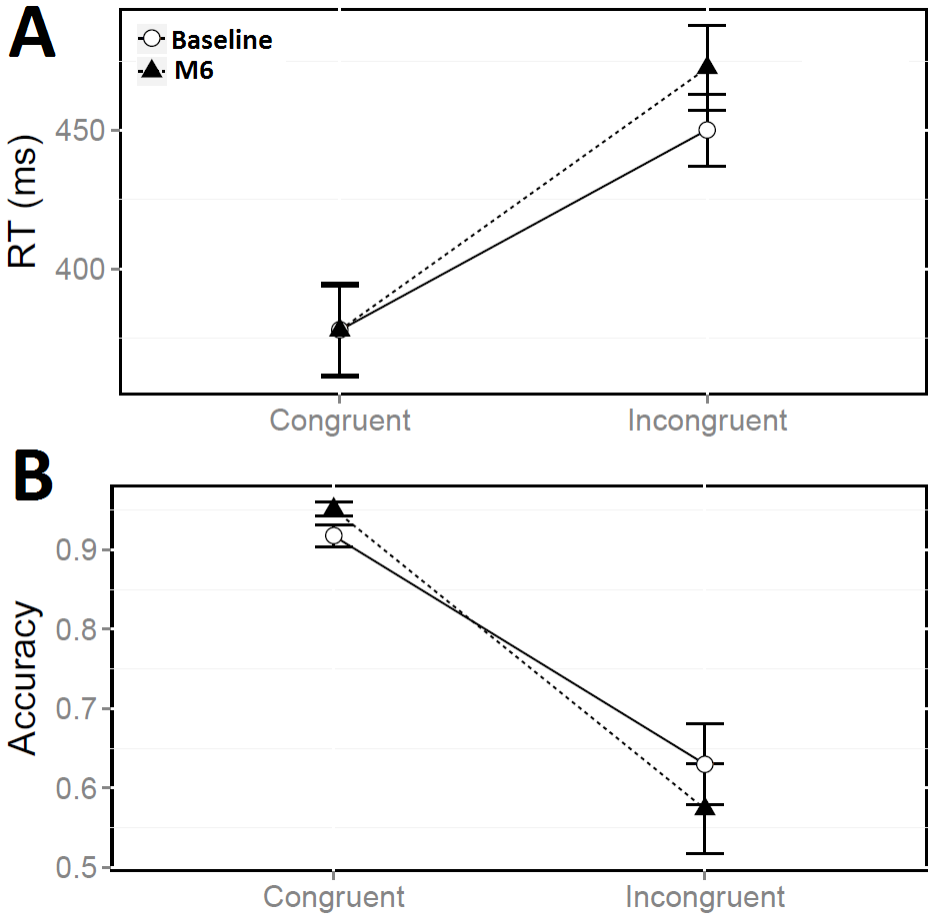

Figure 1: Mean RT (A) and accuracy (B) according to congruence and treatment phase. Error bars represent the standard error of the mean.

3.3. Impulsive action selection

We found no difference between baseline and M6 in accuracy for the first bin of the incongruent situation (Fig. 2; $F(1, 19) = 0.19$, $p = 0.66$). This suggests that patients made just as many impulsive errors 6 months after the introduction of CSAI as they did before. Impulsive action selection is regarded as a key component of the dynamics of cognitive action control, and was our primary focus in this study, along with selective suppression. As the absence of an effect cannot be ruled out solely on the basis of the absence of a significant difference, we computed the 95% confidence interval of the effect between baseline and M6 for impulsive action selection. The mean difference between baseline and M6 was -0.03 (95% CI [-0.09, 0.04]), indicating a negligible decrease in accuracy between baseline and M6. Group differences reported for PD in the Simon task literature are about 0.1 [11, 15, 23]. As the 95% confidence interval for the differences in our study fell below what is usually reported as a meaningful difference, we can safely assume that there were no differences between baseline and M6 on impulsive action selection in our study.

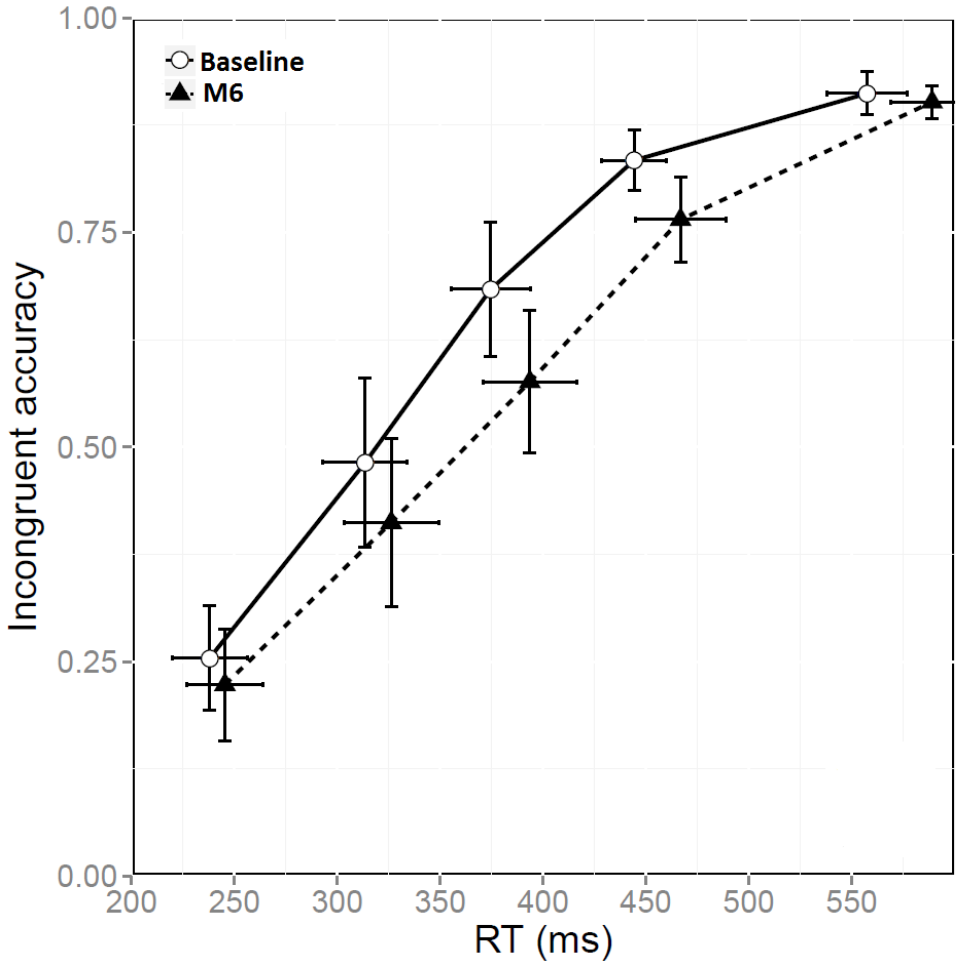

Figure 2: CAF for the incongruent situation, plotted as a function of RT distribution divided into five bins. Accuracy for the first bin indicates the strength of impulsive action selection. Error bars represent the standard error of the mean.

3.4. Suppression of the irrelevant activation

There was no significant difference between baseline and M6 in the slope value of the final bin of the delta plot (Fig. 3; $F(1, 19) < 1$, $p = 0.88$). This suggests that CSAI did not weaken the suppression process, as it remained at its baseline level. As for impulsive action selection, we computed the 95% confidence interval for the mean difference between baseline and M6 to see whether there was a potentially meaningful effect in our data despite the absence of a significant difference. The mean difference between baseline and M6 was -0.01 (95% CI [-0.18, 0.15]). In the literature on conflict control in PD, significant differences are usually about 0.2 [15, 14, 13], which is outside the range of the 95% confidence interval for our data. This strongly supports the absence of an effect between baseline and M6 in our study.

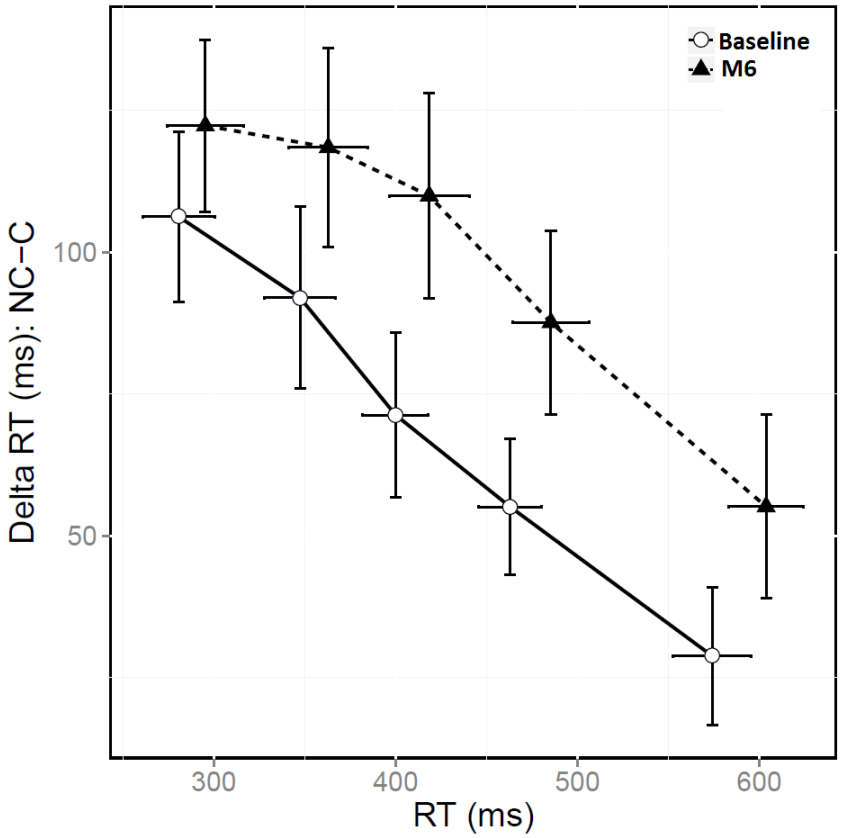

Figure 3: Delta plots showing the congruence effect as a function of RT distribution, divided into five bins. The value of the final slope indicates the strength of selective suppression. Error bars represent the standard error of the mean.

4. Discussion

In the current study, we wanted to check that add-on CSAI has no impact on a key cognitive process (i.e., cognitive action control), and more specifically on the dynamics of this process, as reflected by impulsive action selection and suppression.

Regarding motor improvement, motor fluctuations decreased and oral medication was reduced accordingly, in line with the literature [3, 24, 20]. Regarding cognitive action control, as expected, our results revealed no difference in the congruence effect between baseline and 6 months after the introduction of CSAI. In other words, the cost of conflict resolution was unaffected by the introduction of apomorphine. The primary focus of our study was the effect of CSAI on impulsive action selection (reflected by accuracy for the first CAF bin in the incongruent situation) and suppression (reflected by the last delta plot slope value). We found that patients displayed similar accuracy at baseline and M6 for fast incongruent responses, and exerted equally strong suppression of automatic activations. The 95% confidence intervals for the differences between baseline and M6 on these two measures were not within the range of the

meaningful effects that are usually reported in the literature using the Simon task, arguing in favor of an absence of effect. Thus, our results strongly suggest that CSAI has no impact on impulsive action selection and suppression in patients with mild to moderate PD, in accordance with previous reports of the absence of neuropsychological impairment after CSAI [3, 4, 5].

The absence of a deterioration in cognitive action control may arise from two aspects of CSAI treatment. First, the overall action of the apomorphine molecule may differ from that of other dopamine agonists. Apomorphine is a nonselective dopamine agonist that can interact with both D1-like and D2-like receptors [17], unlike most other antiparkinsonian dopamine agonists, which mainly bind to D2-like receptors. Wylie et al. [14] reported that weaker suppression of automatic activation correlated with higher doses of dopamine agonists (agonists binding to D2-like receptors). As apomorphine differs from the usual agonists, it may well have a different effect on cognitive action control. Another, nonexclusive, hypothesis is that the continuous nature of CSAI treatment, as opposed to the pulsatile doses of standard oral medication, results in greater physiological dopaminergic stimulation without any fluctuation in dose effects. This may stem either from the continuous administration modality of the apomorphine itself or from the overall reduction in oral treatment. In turn, this may maintain a certain level of cognitive performance, such as cognitive action control in the current study. Previous studies investigating the cognitive effect of antiparkinsonian treatments compared the performances of patients between their best (on medication) and worst (off medication) motor conditions. It is therefore difficult to compare the results of other studies with our own, and further investigations are needed to test the hypothesis that continuous versus pulsatile treatment has differential effects on cognitive action control.

Our study had several limitations. The patients in our group were free from cognitive deterioration at baseline and their disease was generally less advanced than that of participants included in previous studies [3, 4, 5]. This raises the question of a potential differential effect of CSAI on cognitive action control in patients with or without cognitive impairment. Thus, although we can hypothesize that CSAI is safe regarding cognitive action control in patients with mild to moderate disease severity, the generalizability of its effect to patients at a more advanced stage of the disease needs to be investigated further. However, it should be noted that the recent study of Borgemeester et al. [16] has shown that CSAI had no negative impact on executive functioning in PD patients with cognitive dysfunction. Another point is that the absence of an effect on cognitive action control in our study has to be offset against the size of the patient sample and the specificity of the task. Confirmation of our results requires similar studies using other cognitive tasks and a larger group of patients. Lastly, it would be very interesting to directly compare the effects of apomorphine and other dopamine agonists on cognitive action control.

5. Conclusion

The present study was the first to investigate the effect of CSAI on the dynamics of cognitive action control. Our results strongly suggest that CSAI has no negative impact on impulsive action selection and suppression in patients with mild to moderate PD. These results are important, as the nonmotor and cognitive effects of antiparkinsonian treatments have a major impact on patients' quality of life (see [1] for a review). Although further studies are needed to confirm the absence of cognitive deterioration with CSAI, our results argue strongly in favor of its safety for cognitive action control.

6. Ethical standards

This study was approved by the ethics committee of Rennes University Hospital and conducted in accordance with the Declaration of Helsinki and current French legislation (Huriet Act).

All the patients gave their informed consent to take part in the study.

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