Deep Brain Stimulation of the Subthalamic Nucleus, but not Dopaminergic Medication, Improves Proactive Inhibitory Control of Movement Initiation in Parkinson's Disease

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Abstract Slowness in movement initiation is a cardinal feature of Parkinson's disease (PD) that is still poorly understood and unsuccessfully alleviated by standard therapies. Here, we raise this major clinical issue within the framework of a novel theoretical model that allows a better understanding of the basic mechanisms involved in movement initiation. This model assumes that movement triggering is inhibited by default to prevent automatic responses to unpredictable events. We investigated to which extent the top-down control necessary to release this locking state before initiating actions is impaired in PD and restored by standard therapies. We used a cue–target reaction time task to test both the ability to initiate fast responses to targets and the ability to refrain from reacting to cues. Fourteen patients with dopaminergic (DA) medication and 11 with subthalamic nucleus (STN) stimulation were tested on and off treatment, and compared with 14 healthy controls. We found evidence that patients withdrawn from treatment have trouble voluntarily releasing proactive inhibitory control; while

DA medication broadly reduces movement initiation latency, it does not reinstate a normal pattern of movement initiation; and stimulation of the STN specifically re-establishes the efficiency of the top-down control of proactive inhibition. These results suggest that movement initiation disorders that resist DA medication are due to executive, not motor, dysfunctions. This conclusion is discussed with regard to the role the STN may play as an interface between non-DA executive and DA motor systems in cortico-basal ganglia loops.

Keywords Response inhibition · Executive control · Reaction time · STN-DBS · Dopamine · Akinesia

Introduction

Akinesia, referred to as slowness and trouble in movement initiation, is one of the most intractable symptoms of Parkinson's disease (PD) [1]. During the last few decades, extensive investigations have been carried out to determine the origin of this deficit. However, highly discordant results have been reported [2] and this symptom is still poorly understood [3]. As a consequence, movement initiation disorders are not easily alleviated by standard therapies [4–6]. Even worse, they can be aggravated by the treatments, for example worsened akinesia [7] or induced impulsivity [8–10]. A prerequisite for current therapeutic strategies is to understand the complexity of the basic mechanisms involved in movement initiation and related dysfunctions. Here, we build upon recent work with healthy participants providing a new theoretical and methodological framework to analyse this major clinical issue.

A common belief is that akinesia is mainly a motor deficit related to dopaminergic depletion. According to the traditional view, the main features of PD are related to

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dysfunctions of the motor circuit, which links the motor cortices to specific territories within the basal ganglia (BG) nuclei [11, 12]. The loss of dopamine (DA) in PD may cause the direct pathway to become less active and the indirect pathway to become more active, resulting in increased subthalamic nucleus (STN) and internal globus pallidus activities, and consequent excessive thalamic inhibition. Accordingly, it has long been assumed that the resulting dysfunction of the thalamocortical feedback route produces akinesia through its action upon motor cortical regions [13, 14].

From the Motor to the Executive Hypothesis

However, this view fails to explain several clinical and experimental observations, such as the fact that lesions of the motor thalamus do not result in akinesia [15] or that globus pallidus lesions do not improve it [16]. Consequently, the dysfunction of the motor circuit cannot alone account for akinesia. We suggest that this symptom would more likely be related to executive impairment.

The first clue was provided by a study which suggested that deficits in movement initiation latency in simple reaction time tasks in PD may be due to dysfunctions occurring earlier than the motor stage [17]. The second clue comes from more recent anatomo-functional models of BG organization, which reveal the involvement of a “hyperdirect pathway” that connects the cortex to the STN directly [18, 19]. This pathway is hypothesized to play an important role in the executive, inhibitory control of responses [20]. The third clue was provided by clinical investigations showing that PD patients are generally found to be dysfunctional on measures of response inhibition [21], supporting the view that executive control over responses is compromised in PD [22, 23]. However, inconsistent observations are reported regarding the nature of this broad deficit: While some authors found that PD patients have difficulties inhibiting an ongoing reaction [22, 24, 25], others suggested an enhancement instead of an impairment of inhibitory control [26]. We assume that these inconsistencies are partly due to the fact that current models of inhibitory control of responses, and derived psychophysical methods, are incomplete and unable to evidence important executive mechanisms ignored so far.

Akinesia as a Possible Consequence of Proactive Inhibitory Control Disorder

The standard model of inhibitory control is based mainly on the postulate that countermanding inappropriate stimulus-driven response impulses rely on phasic, reactive processes triggered by the inappropriate stimulus itself. We showed recently in healthy human participants that tonic, proactive inhibitory processes driven by top-down control entail anticipatory locking of movement-triggering mechanisms in order to prevent automatic responses to upcoming and

Fig. 1 Proactive inhibitory control operates as a gating mechanism acting on movement initiation processes. This functional characteristic clearly differentiates this model from the standard reactive view of inhibitory control. While the standard model assumes that response inhibition relies on phasic, reactive processes triggered by the inappropriate stimulus itself, proactive inhibitory control assumes that refraining from reacting mostly relies on tonic, proactive processes. Proactive inhibition can be released reactively by the appropriate target stimulus or anticipatorily by a predictive cue. In other words, proactive inhibitory control does not only account for the ability to counteract inappropriate actions, it also strongly accounts for the latency of initiation of appropriate movements. (A) Experimental set-up used to assess proactive inhibitory control (cue-target detection task). (B) Dynamics of proactive inhibitory control in healthy subjects. When there is no uncertainty about the upcoming stimulus (a pure condition in which only targets are presented, rarely considered in psychophysical set-ups), no proactive inhibitory control is required. Responses can be triggered automatically. Conversely, when there is uncertainty about upcoming stimuli, tonic response inhibition is required to prevent automatic responses to potentially inappropriate stimuli. Proactive inhibitory control can only be lifted after the stimulus has been identified, when appropriate (if the stimulus is the target or if the stimulus is predictive of its occurrence). Proactive inhibitory control involves the anticipated suppression of the neuronal processes underlying movement initiation. This means that the effect of a simple warning cue consists mainly of generating a phasic signal that unbolts the gate before a target occurs. (C) Behavioural markers of proactive inhibitory control in cue-target protocols. When there is uncertainty, automatic responses are refrained and the target needs first to be identified to allow the release of proactive inhibitory control and, hence, movement initiation. Accordingly, no-cue trials in cue-target protocols show a dramatic increase in reaction time with respect to no-cue trials performed apart in pure blocks. If a warning cue is presented sufficiently in advance of the target (cue-target onset asynchrony ≥ 300 ms), proactive inhibitory control has already been released at target occurrence and fast automatic responses to subsequent stimuli are generated in a similar way to no-cue trials performed apart in pure blocks. The time required to switch from a controlled proactive inhibitory state to a state of automatic reactivity can be estimated by means of the dynamics of cued trials reaction time (adapted from [30, 32])

potentially inappropriate stimuli [27–31]. Even more recently we proposed that proactive inhibition of response is the default mode of executive control [32]. These recent advances are important in several respects. First, they propose a psychophysical method that is able to evidence this hidden face of executive mechanisms. Second, they suggest that proactive inhibitory control determines not only the ability to prevent prepotent responses to potentially inappropriate stimuli, but also the ability to initiate responses to appropriate stimuli (Fig. 1). In other words, along with others [33], the proactive inhibitory control model hypothesizes that healthy participants can switch easily from controlled inhibition of response (anticipated suppression of the neuronal processes underlying movement initiation) to automatic processing of sensorimotor information (unlocked state), depending on their expectations of upcoming events. We assume that an impairment of this mechanism in PD would result in a slowing down of movement initiation. Inspired by former proposals [34, 35] we suggest that akinesia may be viewed as a de-automation symptom resulting from an

impairment in executive, inhibitory functioning. The first goal of the present study is to test this hypothesis. We hypothesize that PD patients might implement proactive inhibitory control inappropriately.

A Dopaminergic Origin of Akinesia?

The dopaminergic origin of akinesia in PD is unclear and needs to be assessed within the framework provided by the proactive inhibitory control model. This is the second goal of the present study. On the one hand, executive dysfunctions are thought to be related to dopaminergic abnormalities in PD [36–38]. On the other hand, it was reported that dopaminergic medication does not fully restore movement initiation disorders as assessed with reaction time tasks [17], and that DA neither influences the efficiency and speed of inhibition nor the efficiency of conflict resolution [8, 39]. Beyond these divergent clinical results, animal studies are also controversial [40]. Nevertheless, Eagle and colleagues showed recently that DA can have opposing functions on inhibitory systems depending on the receptors under scrutiny [41]. If DA is involved specifically in proactive inhibition, we hypothesize that PD patients under dopaminergic treatment should improve movement initiation latency even more when proactive inhibition is required.

Effects and Side-Effects of Deep Brain Stimulation of the Subthalamic Nucleus (STN-DBS): What do They Tell Us About Inhibitory Dysfunctions?

STN-DBS is considered the gold standard for the treatment of advanced PD with levodopa-induced motor fluctuations [42, 43] leading to major improvements in motor symptoms. However, growing evidence suggests that STN-DBS also causes executive inhibitory deficits and impulsive behavior under high-conflict situations [8, 44–46]. In fact, the therapeutic mechanisms of DBS are still not understood completely [47].

It has been proposed that the hyperdirect pathway may be involved in the initiation of voluntary movement; not directly via motor activation mechanisms, but via the inhibition of competing motor programs [48]. In the same vein, a seminal work from Frank and colleagues [8] proposed a neurocomputational model of the BG in which the STN provides a dynamic “hold your horses” signal, temporarily preventing the execution of any response when facing high-conflict decisions. Accordingly, STN-DBS would eliminate the subthalamic NoGo signal and facilitate movements, while also leading, potentially, to cognitive disinhibition and premature responding in situations of high-conflict decisions. However, while the “hold your horses” model accounts robustly for DBS-induced motor impulsivity, it does not explain how the role of STN in executive, inhibitory control may account for akinesia. The proactive inhibitory control model might be

able to. It predicts that STN-DBS does not only modulate reactive processes, but also proactive processes controlling the gating mechanism involved in response initiation. This hypothesis was raised in a recent neuroimaging study from our group, which showed that STN-DBS induces reduced activation not only in the cortical networks responsible for reactive inhibition, but also in the cortical networks responsible for proactive response inhibition [34]. However, neither the experimental task (Go/NoGo) nor the imaging technique (positron emission tomography) allowed an assessment of the dynamics of the top-down control consisting of switching from proactive inhibition of response to automatic reactivity. This is the third goal of the present study. If STN plays a role in proactive inhibitory control, we hypothesize that STN-DBS should improve movement initiation latency even more when proactive inhibition is required.

Materials and Methods

Participants

Three groups participated in this study: 14 PD patients treated with anti-Parkinsonian drugs (MED group: 9 men, 5 women; mean age $\pm$ standard error 57.4 ± 2.3 years), 11 PD patients treated with bilateral STN-DBS for at least 3 months (STIM group: 5 men, 6 women; mean age 60.5 ± 1.7 years), and 14 age-matched healthy controls (CTRL group: 7 men, 7 women; mean age 57.4 ± 1.7 years). The main demographic and clinical characteristics of the patients, the stimulation parameters and the levodopa equivalent dose [49] used, as well as the effects of dopaminergic medication intake and STN-DBS on Unified Parkinson Disease Rating Scale (UPDRS) motor scores are presented in Tables 1 and 2. The patients did not exhibit major signs of tremor and were not demented. No control participant had a history of psychiatric or neurological disease. All participants were right-handed. Visual acuity of all participants was normal or corrected to normal. Participant consent was obtained according to the Declaration of Helsinki and the experimental protocol was approved by the local Ethical Committee in Biomedical Research (comité de protection des personnes sud-est IV, No. CPP 11/025).

General Method of Assessment

As described in Fig. 1, a simple cue–target detection task allows an assessment of the dynamics of proactive inhibitory control. PD patients were tested twice, on consecutive mornings (at around 9 am), with and without treatment (ON and OFF conditions). Control participants were tested only once. The effect of the disease on proactive inhibitory control was assessed by comparing patients OFF treatment (MED group)

Table 1 Demographic and clinical characteristics of the Parkinson's disease patients treated only with dopaminergic medication (MED group)

	Sex	Age (years)	DD (years)	UPDRS III Score		Dopaminergic Medication (mg/day)	LED (mg/day)	Predominant Symptoms
				ON	OFF			
1	F	63	7	4	22	L: 350; E: 1000; Pr: 0.75	482.5	Rigidity, freezing, dyskinesia, postural instability
2	F	67	11	13	32	L: 850; E: 200; Ro: 6	994.5	Freezing, dyskinesia
3	M	60	6	-	29	L: 500; E: 1200; Pr: 3	907	Akinesia/bradykinesia, tremor, freezing
4	M	60	7	12	38	L: 1050; Ro: 16; Ap: 4	1558.5	Dyskinesia, postural instability
5	M	47	6	6	14	L: 750; Pi: 60	810	Rigidity, akinesia/bradykinesia
6	M	61	8	5	25	L: 900; Pi: 150; Am: 200	1100	Akinesia/bradykinesia
7	M	65	14	9	39	L: 1300; Am: 100	1375	Rigidity
8	M	58	8	3	22	L: 1050; Pr: 2.1	1647	Akinesia/bradykinesia
9	M	46	5	22	42	L: 1000; Am: 300; Ra: 1	1400	Tremor
10	F	54	10	2	16	L: 750; Ro: 10; Am: 100	1223	Tremor, dyskinesia, freezing
11	M	61	9	18	39	L: 850; Ro: 20; Am: 100; Ap: 5; Ra: 1	1640	Akinesia/bradykinesia, dyskinesia
12	F	37	8	9	37	L: 700; E: 1750	1081	Akinesia/bradykinesia, tremor
13	M	59	6	6	39	L: 700; Ro: 4	1181	Akinesia/bradykinesia, freezing
14	F	65	15	9	26	L: 575; Ro: 12; Am: 200	1146.75	Freezing, dyskinesia
Mean	57.4	8.6	9.1	30.0			1181.9	
(SE)	(2.3)	(0.8)	(1.6)	(2.5)			(88.0)	

Of note: some data of the UPDRS III cannot be fulfilled owing to a technical problem

SE = standard error; F = female; M = male; DD = disease duration; L = levodopa; E = entacapone; Pr = salt of pramipexole; Ro = ropinirole; Ap = apomorphine; Pi = piribedil; Am = amantadine; Ra = rasagiline; LED = levodopa equivalent dose [49]

to the age-matched control group. The effect of dopaminergic medication on proactive inhibitory control was assessed by comparing MED patients ON and OFF treatment. The effect of STN-DBS on proactive inhibitory control was assessed by comparing STIM patients ON and OFF treatment.

The order of the ON and OFF conditions was counter-balanced across participants. For the MED group, drug withdrawal in the OFF condition started 12 h before testing. For the STN-DBS group, the stimulator was switched off in the OFF condition 30 min before testing, but the usual anti-Parkinsonian drugs were not removed. The fact that they were tested at the same time in the ON and OFF conditions ensured that the effect of dopaminergic medication was identical in both states. For each patient, the gain due to the treatment was estimated by measuring the change of UPDRS motor score. The gain in motor scores was up to 30 %, ensuring that the treatment was effective on motor symptoms (Tables 1 and 2).

Experimental Procedure

The experimental task was adapted from earlier studies performed with healthy participants [28, 29, 32] (Experiment 2 [30]; Experiment 1a and 1b [31]). It consisted of a simple visual reaction time (RT) task. Stimuli were projected on a

screen placed 50 cm away from the participants' eyes. Participants had to answer by pressing a button with the right index finger. Stimulation and data acquisition procedures were programmed using Presentation 14.8™.

While keeping their gaze fixed on a central fixation point (a 1.2° of visual angle cross at the centre of the screen), participants were asked to react as quickly as possible to a visual target that might or might not be preceded by a neutral warning signal (referred to as cue-target trials and no-cue trials respectively). The neutral cue was composed of two peripheral white squares (1.37° of visual angle) located 10° to the left and right of the fixation point (duration 50 ms). The target was a white "X" (0.57° of visual angle) located randomly either 10° to the left or right of the fixation point (duration 50 ms), i.e., at the same location of one of the two squares forming the warning signal. After target presentation a 2000-ms delay was introduced before what is actually considered as the beginning of trial n+1 (starting with a variable 1100–1600-ms delay before possible cue presentation). In cued trials, stimulus onset asynchrony was manipulated so that the cue-target delay varied randomly across three conditions: 150, 350, and 550 ms (referred to as CTOA-150, CTOA-350, and CTOA-550 respectively) (Fig. 1A).

Two blocks of trials were performed. A mixed block in which cue- and no-cue trials were presented randomly, and a

Table 2 Demographic and clinical characteristics of the Parkinson's disease patients treated with deep brain stimulation of the subthalamic nucleus (STIM group)

	Sex	Age (years)	DD (years)	UPDRS III Score		Dopaminergic medication (mg/day)	LED (mg/day)	Stimulation Parameters		TSS (months)	Predominant Symptoms
				ON	OFF			LS (plot/ Hz/ μ s/V)	RS (plot/ Hz/ μ s/V)		
1	M	56	12	14	38	L: 500	475	2-/145/ 90/3.5	5-/145/60/3.5	3	Akinesia/bradykinesia, rigidity
2	F	68	17	3	20	Pr: 1.05	150	1-/160/60/2.8	7-/160/60/3.2	3	Tremor
3	F	62	30	-	30	L: 200; Pr: 2.1	500	2-/60/60/3.8	6-/60/60/3.8	12	Tremor, postural instability
4	M	66	17	15	30	L: 200; Pr: 1.5	350	3-/ 130 /60/3.5	6-/ 130 /90/3.6	60	Akinesia/bradykinesia
5	F	54	7	5	17	L: 150	150	2-/130/60/1.8	6-/130/60/2.3	3	Rigidity
6	M	59	19	15	35	L: 800	800	2-/70/60/4	6-/70/60/4	3	Tremor, freezing
7	M	64	17	8	30	L: 300	300	2-/130/60/2.6	5-/130/60/3.1	3	Akinesia/bradykinesia
8	F	63	17	4	28	L: 150	150	2-/145/60/2.7	7-/145 /60/3.2	3	Tremor, postural instability
9	F	62	10	8	24	L: 500	500	2-/130/60/2.6	6-/130/60/2.8	3	Rigidity, postural instability
10	M	63	11	-	-	L: 800; Pr: 1.5	950	2-/145/90/2.6	6-/145/60/2.9	63	Akinesia/bradykinesia
11	F	49	7	9	31	L: 175; Pr: 2.1; Am: 200	675	1-/130/60/2.4	5-/130 /60/3.1	11	Akinesia/bradykinesia, postural instability
Mean (SE)		60.5 (1.7)	14.9 (2.0)	8.4 (1.4)	27.2 (1.7)		454.5 (81.5)			14.3 (6.4)	

Of note: some data of the UPDRS III cannot be fulfilled owing to a technical problem

SE = standard error; M = male; F = female; DD = disease duration; UPDRS = Unified Parkinson Disease Rating Scale; L = levodopa; Pr = salt of pramipexole; Am = amantadine; LED = levodopa equivalent dose [49]; LS = left side; RS = right side; TSS = time since surgery

pure-block in which only no-cue trials were presented. Participants were instructed to try to comply with a maximum error rate of 10 %. When an overt response was given before target occurrence (false alarm), too soon after target occurrence (abnormally short RT: RT < 150 ms), or too long after target occurrence (omission: RT > 1000 ms), the trial was aborted immediately, and an error signal was displayed on the screen. The experimental session began with a training pure-block consisting of 120 no-cue trials followed by a mixed training block of 40 trials. Actual recordings were performed in 2 following blocks (one pure-block of 100 trials and one mixed block of 246 trials). The order of these blocks was counterbalanced across participants and treatment conditions using a Latin square design.

Statistical Analyses

First, between groups comparisons were performed using unpaired two-sample *t* tests to ensure that the three groups were not different regarding the mean age of the participants, and to test for possible clinical differences between the two groups of patients. The effect of the treatment was estimated within each group of patients by means of paired two-sample *t* tests.

Second, analyses of variance (ANOVA) were performed on mean RTs (excluding RTs exceeding three standard deviations). The effect of the disease was assessed by means of a 2 Groups (MED-OFF, CTRL) $\times$ 5 Trials (no-cue mixed-block, no-cue pure-block, CTOA-150, CTOA-350, CTOA-550) ANOVA with repeated-measures. The effect of dopaminergic medication was assessed by means of a 2 Treatment (MED-ON, MED-OFF) $\times$ 5 Trials (no-cue mixed-block, no-cue pure-block, CTOA-150, CTOA-350, CTOA-550) ANOVA with repeated-measures. The effect of STN-DBS was assessed by means of a 2 Treatment (STIM-ON, STIM-OFF) $\times$ 5 Trials (no-cue mixed-block, no-cue pure-block, CTOA-150, CTOA-350, CTOA-550) ANOVA with repeated-measures. Post hoc comparisons were performed when necessary using Newman–Keuls tests. All tests were two-sided and considered significant when $P < 0.05$.

Third, similar analyses were performed to assess the error rates. False alarms and abnormally short RTs were pooled together (anticipations). Omissions were considered separately. The percentages of anticipations and omissions were submitted to the same ANOVA (after ArcSine transform), with the exception that only 3 types of Trials were considered (no-cue mixed-block, no-cue pure-block, cue).

Results

Characteristics of Participants

The two patient groups and the control group were matched for age (CTRL: 57.4 ± 1.7 vs MED: 57.4 ± 2.3 vs STIM: 60.5 ± 1.7 years old; $p > 0.21$). The duration of the disease was greater in the STIM group than in the MED group [STIM: 14.9 ± 2.0

vs MED: 8.6 ± 0.8 years, $t(23) = 3.2$, $p < 0.001$]. The levodopa equivalent dose per day of dopaminergic drugs [49] was greater in the MED group than in the STIM group [MED: 1181.9 ± 88 vs STIM: 454.5 ± 81.5 mg/day; $t(23) = 5.91$, $p < 0.001$]. The ON condition improved the motor score at the UPDRS for the two patient groups [by 71.1 % for the MED group, $t(11) = 10.50$, $p < 0.001$; and by 69.2 % for the STIM group, $t(7) = 12.64$, $p < 0.001$].

Fig. 2 Reaction times (means and standard deviation) for patients without treatment versus healthy matched controls (A), for patients with and without dopaminergic medication (B), and for patients with or without deep brain stimulation of the subthalamic nucleus (STN-DBS) (C). (A) While patients are not impaired in their ability to take advantage of the presentation of a warning cue to improve reaction time (RT) to the upcoming target, they reveal a strong deficit in RT with respect to controls in the condition, which is supposed to involve fast automatic reactions. According to the proactive inhibitory control model of executive control, this pattern of results suggests that Parkinson's disease (PD) patients are specifically impaired when proactive inhibitory control must be released internally before entering the task. (B) Dopaminergic medication induces an overall reduction of RT, consistent with motor effects, but does not fully restore the executive deficit observed for no cue trials performed apart in a pure block design. (C) STN-DBS restores a normal pattern of responsiveness in the pure condition in which PD patients are supposed to voluntarily release proactive inhibitory control. Note that for clarity reasons the vertical scales are not the same in the different parts of the figure.

* $p < 0.05$; ns = not significant

Effect of PD

Errors

The percentage of anticipations was smaller in no-cue trials than in cue-target trials [no-cue mixed-block: 0.2 ± 0.1 vs no-cue pure-block: 0.5 ± 0.2 vs cue-target trials: 7.0 ± 1.2 %; $F(2, 52) = 42.45$, $p < 0.001$]. PD patients without medication made more anticipations than controls [OFF-MED: 3.3 ± 1.6 vs CTRL: 1.8 ± 0.9 %; $F(1, 26) = 5.15$, $p < 0.05$]. No significant interaction was observed ($p = 0.90$).

Conversely, the percentage of omissions was larger in no-cue mixed-block than in cue-target trials [no-cue mixed-block: 2.6 ± 1.4 vs no-cue pure-block: 1.2 ± 0.5 vs cue-target trials: 1.1 ± 0.7 %; $F(2, 52) = 3.64$, $p < 0.05$]. Patients also made more omissions than controls [OFF-MED: 3.1 ± 1.8 vs CTRL: 0.2 ± 0.2 %; $F(1, 26) = 7.64$, $p < 0.01$]. No significant interaction was observed ($p = 0.16$).

Reaction Time (Fig. 2A)

A significant group $\times$ trial interaction was observed [$F(4, 104) = 2.75$, $p < 0.05$]. In controls, the pattern of RTs was the same as reported previously with younger participants (Fig. 1C). Short cue-target delays (CTOA-150) did not provide any RT benefit with respect to the no-cue mixed-block condition ($p = 0.78$). Conversely, longer cue-target delays showed shorter RT than the no-cue mixed-block condition (CTOA-350: 328.8 ± 9.8 vs CTOA-550: 308.3 ± 9.4 vs no-cue mixed-block: 404.2 ± 9.5 ms, $p < 0.001$). However, RTs for CTOA-550 did not go below RTs for the no-cue pure-block condition (no-cue pure-block: 313.2 ± 8.5 ms, $p > 0.24$). Interestingly, PD patients did not differ from controls for cued trials (CTOA-150: 417.5 ± 15.1 , CTOA-350: 357.6 ± 18.3 , CTOA-550: 329.7 ± 15.7 ms for OFF-MED patients, $p > 0.35$). They showed increased RTs with respect to healthy participants only for no-cue trials, whatever the block (pure-block: 382.3 ± 26.8 , mixed-block: 453.9 ± 14.1 ms for MED-OFF patients, $p < 0.05$). Of particular interest is the observation that, in PD patients, RTs were greater in the no-cue pure-block condition than in the CTOA-550 condition ($p < 0.001$) and in the CTOA-350 (with a p -value approaching the conventional statistical threshold: $p = 0.06$).

Effect of Dopaminergic Medication

Errors

The percentage of anticipations was larger in cue-target trials than in no-cue trials [no-cue mixed-block: 0.4 ± 0.2 vs no-cue pure-block: 1.1 ± 0.4 vs cue-target trials: 9.3 ± 2.3 %; $F(2, 26) = 25.33$, $p < 0.001$]. No effect of dopaminergic medication and no group $\times$ trial interaction were observed ($p > 0.31$).

Conversely, the percentage of omissions was larger in no-cue trials than in cue-target trials [no-cue mixed block: 4.5 ± 2.5 vs no-cue pure-block: 3.0 ± 2.1 vs cue-target trials: 1.8 ± 1.2 %; $F(2, 26) = 16.06$, $p < 0.05$]. No effect of dopaminergic medication and no group $\times$ trial interaction were observed ($p > 0.43$).

Reaction Time (Fig. 2B)

A significant effect of trial was observed [$F(4, 52) = 30.87$, $p < 0.001$]. It revealed the same pattern as the one described above (no-cue mixed-block: 440.9 ± 14.9 vs CTOA-150: 403.7 ± 13.3 vs CTOA-350: 341.5 ± 16.5 vs CTOA-550: 316.6 ± 13.5 vs no-cue pure-block: 362.8 ± 24.1 ms, all p -values of interest < 0.01). PD patients exhibited faster responses when medicated [OFF-MED: 388.2 ± 21.5 vs ON-MED: 358.0 ± 18.7 ms; $F(1, 13) = 4.91$, $p < 0.05$]. Importantly, no interaction was observed between the two factors ($p = 0.91$).

Effect of STN-DBS

Errors

The percentage of anticipations was larger in cue-target trials than in no-cue trials. In no-cue trials it was larger in control than in mixed block [no-cue mixed-block: 0.4 ± 0.2 vs no-cue pure-block: 1.5 ± 0.5 vs cue-target trials: 4.5 ± 0.7 %; $F(2, 20) = 30.76$, $p < 0.01$]. No effect of STN-DBS and no group $\times$ trial interaction were observed ($p > 0.34$).

Conversely, the percentage of omissions was larger in no-cue trials than in cue-target trials [no-cue mixed-block: 8.6 ± 3.1 vs no-cue pure-block: 2.5 ± 1.0 vs cue-target trials: 3.2 ± 1.8 %; $F(2, 20) = 8.35$, $p < 0.01$]. No effect of STN-DBS and no group $\times$ trial interaction were observed ($p > 0.59$).

Reaction Time (Fig. 2C)

A significant interaction treatment $\times$ trial was observed [$F(4, 40) = 3.69$, $p < 0.01$]. When STN-DBS was OFF patients exhibited a pattern of results entirely consistent with the one depicted earlier to assess the effect of the disease (Fig. 2A) (no-cue mixed-block: 526.2 ± 28.5 vs CTOA-150: 484.1 ± 28.1 vs CTOA-350: 432 ± 27.1 vs CTOA-550: 397.9 ± 24.1 vs no-cue pure-block: 446.7 ± 29.9 ms, all p -values of interest < 0.01). The only change observed when STN-DBS was turned ON concerns no-cue pure-block trials: RTs were shorter than when STN-DBS was OFF (no-cue pure-block in ON-STIM condition: 406.8 ± 21.5 ms, $p < 0.001$) and were no longer different to CTOA-550 (CTOA-550 in ON-STIM condition: 407.7 ± 22.6 ms, $p = 0.98$).

Discussion

We found impaired ability of patients to release proactive inhibitory control leading to slowness in movement initiation. Yet, this deficit was observed only when the release of proactive inhibition had to be driven internally, not when it was triggered by an external warning cue. Dopaminergic medication broadly reduced RTs, but did not restore the internal control of the default proactive inhibition of response. Conversely, STN-DBS has no global effect on movement initiation latency. However, it specifically restored the ability to voluntarily release proactive inhibition, i.e., to switch to an automatic mode of sensorimotor processing when appropriate.

Proactive Inhibitory Control Impairment in PD

Not surprisingly, PD patients without treatment reveal overall longer RTs than healthy control participants and produce more omissions, consistent with difficulties in movement initiation. However, they are not equally impaired for all conditions. Patients behave like controls when a warning cue informs them about the occurrence of the target, meaning that they are able to take advantage of cue presentation to improve RT to the upcoming target. According to the proactive inhibitory control model this suggests that the ability to release inhibitory control in response to an exogenous cue is preserved. Nonetheless, PD patients are impaired with respect to controls when no cue is provided before target presentation. Of particular interest is the pure condition in which participants know beforehand that only targets might be presented, i.e., when no proactive inhibitory control is required. In healthy controls, this condition provides the shortest RTs as responses are triggered on the basis of automatic motor activations, as demonstrated consistently with younger participants [28–32]. This is not the case for PD patients who show increased RTs with respect to cued trials with long stimulus onset asynchrony. This critical observation suggests that PD patients are impaired in their ability not to implement proactive inhibitory control in situations where automatic reactions are allowed. To some extent, this is in agreement with the hypothesis according to which akinesia may be viewed as a de-automation symptom resulting from an impairment in executive, inhibitory functioning [35]. This conclusion is in accordance with the broad idea that PD patients are locked into a control mode of executive functioning, at least when no exogenous cue allows the release of this control. It is also reminiscent of the acknowledged difficulty of PD patients to initiate internally generated movements with respect to externally cued movements [50, 51] (Fig. 3). From these observations, it can be asserted that dysfunctions in the control of proactive inhibition of response contribute to akinesia

by inappropriately slowing down or gating response triggering. The impairment of this mechanism may account for broader disorders of movement initiation. For instance, the results of the present study may provide new insights into the problem of gait initiation encountered by most PD patients with freezing of gait. Consistent with our hypothesis, the problem with central drive and automaticity of movement leading to gait initiation disturbances is often associated with broad executive dysfunctions, as reviewed recently by Nutt and colleagues [52].

The Respective Effects of Dopaminergic Medication and STN-DBS

Not surprisingly, dopaminergic medication improved RTs in the present study. However, it improved RT equally for all conditions, meaning that its effect is null on proactive inhibitory control processes (Fig. 2B). Our results are partly consistent with the view that purely motor effects, mediated by DA, contribute broadly to slow down movement initiation speed [13, 53]. However, they also suggest that the motor energizing role for DA [1] does not fully account for akinesia (Fig. 3).

The effect of STN-DBS is clear in the present data. It specifically affects the pure condition in which PD patients are supposed not to implement proactive inhibitory control. STN-DBS restores a normal pattern of responsiveness in this condition, i.e., allows reacting automatically to upcoming events (Fig. 2C). In other words, STN-DBS would specifically act by regaining control of the state of “self-initiated automaticity”. The observation that STN-DBS does not significantly improve RTs when the release of proactive inhibitory control is triggered by exogenous cues is also coherent with a recent study showing that STN-DBS improves intrinsic, but not phasic, alertness [54]. This pattern of results strongly suggests that the effect of STN-DBS on motor responsiveness is executive and not only purely motor (Fig. 3).

It is noteworthy that, while there is a clear difference between STN and DA replacement therapies in our experiment, the clinical improvement as assessed with the motor subscale of the UPDRS is identical for both therapeutic approaches (DA replacement therapy induced improvement: 71.1 %; STN-DBS induced improvement: 69.2 %). Yet, it must be acknowledged that this standard clinical evaluation is based on various motor tasks that are not restricted to the evaluation of slowness and trouble in movement initiation [1]. More generally, the definition of akinesia remains ambiguous, and its clinical assessment does not distinguish it from hypokinesia and bradykinesia [3]. This introduces potential confounds between movement initiation and movement execution impairments in PD. While the executive and motor effects of STN and DA replacement therapies

Fig. 3 Schematic illustration of the respective effects of dopaminergic medication and deep brain stimulation of the subthalamic nucleus (STN-DBS) on proactive inhibitory control impairment in Parkinson's disease. (A) In healthy subjects, proactive inhibition over movement triggering mechanisms is the default state of executive control. It allows preventing undesired fast automatic responses to stimuli to save time for slow volitional response preparation. Proactive inhibition can be released either anticipatorily by internal control (when the context encourages fast automatic reactions to any upcoming event) or reactively by external cues (e.g., warning signals). (B) In the Parkinsonian state, disorders of movement initiation assessed by RT and omissions are mainly due to two types of disorders: a global effect acting on motor output functions and an executive effect acting specifically on the internal control of proactive inhibition. (C) Dopaminergic medication restores the motor output function, but not the internal control of proactive inhibition. (D) STN-DBS specifically restores the internal control of the default proactive inhibition of response triggering mechanisms. In other words, STN-DBS allows regaining control of the state of “self-initiated automaticity”

can be disentangled experimentally they may not be obviously separable clinically, leading to the impression that STN-DBS and DA replacement have similar clinical effects. Thus, our results call for refining the assessment of movement initiation disorders.

Relevance to the Pathophysiology of Akinesia

The classic pathophysiological model of the BG does not account for all motor and executive clinical features of the disease [3]. On the basis of the present results, as well as

former studies depicting the functional anatomy of proactive inhibitory control in healthy participants, it is tempting to speculate on the cerebral networks which dysfunction may cause akinesia in PD.

In healthy participants, the proactive inhibitory control model both assumes tonic proactive activity related to sustained inhibition and phasic reactive activity related to the command signal that triggers the release of tonic inhibition [27–32]. This view is consistent with the involvement of the slow indirect pathway/striatal loops and the fast hyperdirect pathway/STN loops in inhibitory control [8, 34, 55–57]. It is reminiscent of 1) the cortico-striatal control account of how the brain gradually implements response thresholds by increasing activation from cortex to striatum in healthy participants [58]; 2) of the cortico-STN control account of how the brain relays fast reactive changes in the motor circuitry [59–62]; and 3) of the supplementary motor complex control account of how the brain switches from controlled to automatic sensorimotor processing [61]. It is noteworthy that areas outside motor regions, like the dorsomedian frontal cortex (BA 9/10), the posterior cingulate cortex (PCC-/ventral precuneus) and the inferior parietal lobule, also play a critical role in the control of proactive inhibition [30, 31]. Importantly, the whole network is already known to support executive functions [63, 64]. The pattern of anatomical and functional connectivity of these non-motor regions of the cortex with the non-motor regions of the STN is compatible with a possible influence of executive origin of the former on the latter via the hyperdirect pathway [65–68]. Besides, the fact that non-motor territories of the STN are connected to the motor ventrolateral thalamus [65] strongly suggests that the STN may, indeed, act as a direct interface between executive and motor systems. In other words, we suggest that in healthy participants the STN may relay not only a fast reactive NoGo signal to inappropriate stimuli from pre-supplementary area (pre-SMA) [8, 59], but also a control signal that appropriately triggers the release of the default locking state of executive control from executive areas [32].

It is acknowledged that there is an abnormal activity within the aforementioned brain regions in PD that might account for akinesia. For instance, impaired activation of the medial frontal areas and putamen accounts for the difficulties PD patients have in initiating movements [69], with concomitant over-activity of primary sensorimotor cortex [70]. SMA is hypoactivated and SMA-putamen connectivity is abnormal during motor behavior in PD patients [71, 72], as well as in animal models of PD [14]. Less stimulus-induced deactivation of the PCC/precuneus and impaired connectivity between dorsomedian frontal cortex and striatum are also symptomatic of executive disorders as assessed by response latency [73]. Interestingly, a reversed pattern of brain activity (i.e., less activation) for the PCC, the inferior parietal lobe and the pre-SMA leads to difficulties withholding

responses in an explicit inhibitory task [34]. This, therefore, suggests that abnormal cortical activity in these executive and motor networks underlies abnormal proactive inhibitory control in PD. In the present study, STN-DBS restored normal internal control of proactive inhibition (Fig. 3), as assessed behaviourally in patients without impulsive side effects. Theoretically, STN-DBS might equally disrupt the indirect and hyperdirect pathways, with subsequent potential effects on both slow tonic and fast phasic brain activity. It is therefore likely that STN-DBS acts by restoring normal cortico-basal tonic activity in the executive and motor networks. It is as likely that STN-DBS acts by facilitating specifically the phasic activity supporting switches from controlled to automatic sensorimotor processing. Both types of presumed effects are expected to modulate the ability to initiate movements. However, direct assessment remains challenging because fMRI is rarely performed in implanted patients for safety reasons, while positron emission tomography does not allow event-related analysis to separate in-time proactive and reactive brain activations.

Relevance to the Neurochemical Bases of Akinesia

The present study indicates that dopaminergic depletion in PD does not fully account for akinesia, and even that dopaminergic medication does not fully restore it. The issue of which neurotransmitters are involved in the process is thus raised. Converging clues from healthy participants and animal studies pinpoint the possible role of the cholinergic, as well as the noradrenergic, system.

First, nicotine, a cholinergic agonist, was found to improve response latency in cue–target detection tasks by enhancing the cognitive brain mechanisms specifically involved in conditions where no extrinsic cue is provided [74, 75]. Consistent with our results, the benefit in response latency was found to rely on the deactivation of the default activity of the dorsomedian frontal cortex, the precuneus and the PCC [75, 76]. Second, the design used in this study was adapted from a classical task well known to engage the locus coeruleus–norepinephrine network [77–80]. There is no clear consensus about the exact role played by the coeruleus–norepinephrine system, but it is agreed that it supports a key modulatory role in prefrontal cortical function and executive control, including response inhibition [81–85]. As response inhibition and movement initiation are intrinsically related [32], the ability to trigger goal-directed movements would thus strongly rely on the noradrenergic system. Consistent with this hypothesis, Minzenberg and colleagues [86] showed that modafinil improves sensorimotor processing speed by modulating activity in structures overlapping the network previously identified in the control of proactive inhibition of response [30, 31].

In PD, or animal models of the disease, there is now considerable evidence for altered noradrenergic and cholinergic

neurotransmission that may occur at early stages and contribute to cognitive and motor impairments [87–90]. In other terms, the neurochemical bases of executive dysfunction and related deficits in movement initiation in PD are likely to be multifactorial and associated with DA, noradrenaline, and cholinergic deficits. Further studies will have to assess more directly the respective roles of these neurochemical systems in the genesis of akinesia. Their results could change current therapeutic strategies and open up new horizons regarding the pharmaceutical treatments, which may complement standard medication.

Further clarification of the functions, neurochemical bases, and pathophysiology of the BG is still a significant challenge. From a clinical point of view, assessing akinesia is also still a significant challenge. On the one hand, it still needs a narrowed and consensual definition to avoid potential confounds between movement initiation and movement execution impairments in PD. On the other hand, it needs to be considered along with other symptoms, which may not be independent. Akinesia may not be the single outcome of proactive inhibitory control disorders. Clinical symptoms like akinetic freezing (not restricted to freezing of gait) or impulsivity (possibly linked to the inability to implement proactive inhibition) may represent the opposite ends of the same continuum of proactive inhibitory control dysfunction. We hope that the clinical findings described in this article will suggest theoretical and methodological lines of inquiry for future studies that will contribute to resolving these issues.

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