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Original Articles

Interaction of Noradrenergic Pharmacological Manipulation and Subthalamic Stimulation on Movement Initiation Control in Parkinson's Disease



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ABSTRACT

Background: Slowness in movement initiation (akinesia) is a cardinal feature of Parkinson's disease (PD), which is still poorly understood. Notably, akinesia is restored by subthalamic nucleus deep brain stimulation (STN-DBS) but not fully reversed by current dopaminergic treatments. It was recently suggested that this disorder is of executive nature (related to inhibitory control of response) and of non-dopaminergic origin (possibly noradrenergic).

Objective: To test the double hypothesis that: 1) the ability to control movement initiation is modified by noradrenergic neurotransmission modulation, and 2) this effect is mediated by the regulation of STN activity. **Methods:** Sixteen STN-DBS PD patients were enrolled in a placebo-controlled study investigating the effects of noradrenergic attenuation by clonidine (α -2-adrenergic receptor agonist). Movement initiation latency was assessed by means of a cue-target reaction time task. Patients, who remained on their chronic dopaminergic medication, were tested on four sessions: two with placebo (ON- or OFF-DBS), and two with a 150 μ g oral dose of clonidine (ON- or OFF-DBS).

Results: In the OFF stimulation condition, patients were locked into a mode of control maintaining inappropriate response inhibition. This dysfunctional executive setting was overcome by STN-DBS. Clonidine, however, was found to impair specifically the ability to release inhibitory control in the ON-DBS state.

Conclusions: Overall our results suggest an important implication of the noradrenergic system in the pathophysiology of akinesia in PD. Reducing the noradrenergic "tonus" may even block the positive action of STN-DBS on akinesia, suggesting, at least by part, a noradrenergic-dependent STN-DBS efficiency.

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Introduction

Parkinson's disease (PD) is a progressive degenerative disorder of the central nervous system characterized by major motor symptoms, but also by various non-motor symptoms [1–3]. PD is associated with major dopaminergic depletion, yet, the neuro-pathophysiology of the disease involves more than dopamine cell loss within the midbrain [4–7]. This multifaceted aspect of the disease does not ease diagnosis, nor does it facilitate targeted therapy [8–12]. Among the cardinal symptoms of the disease, akinesia is illustrative of this problem. Indeed, akinesia, which

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refers to slowness and dysfunction in movement initiation [13], is still poorly understood and unsuccessfully alleviated by standard therapies. In a previous study [14], we suggested that movement initiation disorders that resist dopaminergic medication are due to executive, inhibitory, not motor, dysfunctions. Indeed, we observed that PD patients were impaired in their ability to gate movement initiation in anticipation of external stimulation to prevent premature or erroneous responses to upcoming events when the context is uncertain. Specifically, PD patients were found to maintain inappropriate proactive response inhibition in situations that did not require action restraint. This deficit was restored by deep brain stimulation of the subthalamic nucleus (STN-DBS), but not by dopaminergic medication. These findings emphasize the role of the STN as an interface between executive and motor systems that support switching from controlled to automatic sensorimotor processing. However, these results left the question of the neurochemical basis of akinesia in PD unanswered.

A growing body of evidence points to the possible role of the noradrenergic system in proactive control of movement initiation and related dysfunctions. First, the caudo-rostral degeneration theory assumes that the noradrenergic system is depleted in PD before the dopaminergic system [15]. Given that the locus coeruleus (LC), the major structure for brain synthesis of noradrenaline (NA), projects to the STN [16–18], it is likely that STN activity is directly modulated by the NA system [19,20]. Although assessing direct noradrenergic brain activity in humans is tricky in the absence of specific PET tracer, consistent clues are provided by pharmacological studies in humans [21–24] and animals [19,25–27]. For instance, it has been shown that gait disorders could also be partly related to a dysfunction of the NA system as methylphenidate improves gait hypokinesia and freezing in PD patients [21,23]. However, as methylphenidate modulates both dopaminergic and noradrenergic neurotransmission, a specific involvement of the NA system is still hypothetical. In parallel, animal studies have only evidenced a direct and undisputable role of NA in the discharge pattern of the STN [19,26]. Here, we analyzed the ability of PD patients to control movement initiation in a placebo-controlled study testing the interaction of STN-DBS and NA neurotransmission modulation by means of clonidine, a specific $\alpha 2$ adrenergic receptor (AR) agonist.

Materials and methods

Participants

Sixteen parkinsonian patients (aged 59.3 ± 5.2 years old, 4 females, with normal or corrected-to-normal vision) treated with bilateral STN stimulation participated in the experiment. The implantation of the electrodes (Model 3389; Medtronic, Minneapolis, MN, USA) was performed under local anesthesia, guided by stereotactic magnetic resonance imaging (MRI), and microelectrode recordings. The accurate placement of the electrodes was confirmed on postoperative CT scan. The electrodes were connected to a pulse generator (Kinetra or Solettra, Medtronic, Minneapolis, MN, USA). The main demographic and clinical characteristics of the patients, the stimulation parameters used, the levodopa equivalent dose, and the effects of STN stimulation on the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores are presented in Table 1. The patients did not exhibit major signs of tremor and were not demented (MATTIS > 130). Of note, two patients (P3, P8) presented pathological gambling and compulsive shopping tendencies while one (P14) reported dopaminergic addiction and nocturnal hyperactivity well before STN-DBS surgery (at least three years ago). These symptoms have been totally suppressed by stopping dopaminergic agonists. Furthermore, all patients were submitted before the experiment to the Ardouin scale [28]. Hyperdopaminergic abnormalities were not reported in any patient.

Participant consent was obtained according to the code of ethics of the World Medical Association (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, N° CPP 12/039).

General method of assessment

The behavioral task was reproduced from Favre and colleagues [14]. This experiment was intended to test the ability of PD patients to initiate simple movements in response to visual targets while maintaining their capacity to refrain from reacting to other visual stimulations. As demonstrated in previous studies, this can be achieved by using a simple cue-target reaction time (RT) task, provided

Table 1
Demographic and clinical characteristics of the Parkinson's disease patients treated with deep brain stimulation of the subthalamic nucleus.

Patient	Sex	Age (years)	DD (years)	UPDRS III		LED (mg/day)	Stimulation parameters		TSS (months)	Predominant symptoms
				ON ^a	OFF ^a		LS (plot/Hz/ μ S/V)	RS (plot/Hz/ μ S/V)		
1	H	59	10	13	33	350	1–/130/60/3.4	9–/130/60/3.5	8	Dysarthria, dyskinesia
2	H	61	14	23	48	465.5	2–/130/60/3.2	7– and 6–/130/90/3	51	Freezing, postural instability, hypertonia
3	H	61	7	7	23	399	3–/130/65/3.25 mA	2–/130/65/3 mA	6	Freezing
4	H	50	26	6	19	160	1–/130/90/3.3	6–/130/90/3.3	35	Dystonia
5	H	65	12	8	20	450	2–/130/60/3.5	5–/130/90/3.6	36	Dyskinesia, mild akinesia
6	F	64	24	20	24	880	2–/130/60/3.5	5–/130/60/3	81	Dyskinesia
7	F	64	15	12	24	660	3–/160/90/3.4	7–/160/90/2.9	34	Bradykinesia,
8	H	58	12	18	44	300	1–/130/60/3	5–/130/60/3.2	42	Akinesia, postural instability
9	F	61	10	10	30	0	2–/130/60/2.5	10–/130/60/2.9	8	Dystonia
10	H	61	14	29	50	1160	2– and 1–/130/90/3.6	5–/130/90/3.6	61	Facial dyskinesia, dysarthria
11	F	65	9	12	18	150	2–/130/60/2.6	11–/130/60/2.8	6	Mild akinesia, mild dyskinesia,
12	H	65	12	4	23	660	2–/160/90/2.6	6–/160/90/2.4	53	Mild akinesia
13	H	55	14	10	36	560	2–/130/60/2.4	10+ and 11–/130/60/2.5	4	Dyskinesia, mild rigidity
14	H	48	12	14	38	300	11–/160/90/3.6	1– and 2+/160/60/2.9	3	Mild tremor
15	H	56	12	2	6	1542.5	3– and 2–/130/90/2.9	11–/130/60/3.5	3	Akinesia, rigidity
16	H	56	7	13	31	1275	3–/160/90/3.6	11–/160/60/3	5	Mild tremor
Mean		59.3	13.1	12.5	29.2	582			27.2	
SE		5.2	5.2	7.1	11.9	433.5			25.2	

DD = disease duration; UPDRS III = motor score at the Unified Parkinson Disease Rating Scale; LED = levodopa equivalent dose [85]; TSS = time since surgery; M = male; F = female; SE = standard error; LS = Left Side; RS = Right Side.

^a UPDRS III scores represent ON and OFF STN-DBS states while patients were screened under their usual dopaminergic medication for both DBS conditions.

that some methodological requirements have been satisfied [29–31]. Specifically, the ability to react to visual stimuli was assessed in separate blocks of trials in which only visual targets were presented (inducing no uncertainty about upcoming stimuli, i.e., no need for subjects to refrain from reacting). In this condition, short RTs are expected because subjects can react automatically to any upcoming event. This condition represents the control condition in which subjects are supposed not to implement proactive inhibitory control. The ability to refrain from reacting to non-targets was assessed on the basis of other blocks of trials mixing targets and cues (inducing uncertainty about upcoming stimuli, i.e., requiring proactive inhibitory control). To this end, the analysis of RT is complementary to classical analyses of commission and omission errors. Indeed, when a target is not preceded by a cue in this uncertain context, proactive inhibitory control can only be lifted after the visual target has been identified, leading to a dramatic increase in RT. Manipulating the time separating cue presentation from target occurrence in cued trials (cue-target delay) allowed the assessment of the dynamics of release of proactive inhibitory control. Indeed, in this case, proactive inhibition can be released by the predictive cue, leading to a rapid decrease in RT, which pinpoints the switch from controlled to automatic sensorimotor processing (Fig. 1).

PD patients were tested in the morning (at around 9 am) on two consecutive days, with and without STN-DBS treatment (ON and OFF conditions) while taking their usual anti-Parkinsonian drugs. The order of the ON and OFF conditions was counterbalanced across participants. The stimulator was switched off in the OFF condition 30 min before testing. The fact that patients were tested at the same time schedule in the ON and OFF conditions ensured that the effect of dopaminergic medication was identical in both states (see Table 1 for the demographic characteristics).

Apparatus and procedure

A panel equipped with light-emitting diodes (LEDs – Ø5 mm, 8800 mcd) was used to present the visual stimuli. One LED was placed in the centre of the panel and set at the subject's eye level. This served as a fixation point for the eyes. The target stimuli were composed of nine LEDs forming a diamond (3.44° of visual angle) located 16° to the left or right of the fixation point (duration 50 ms). The cue was composed of eight LEDs forming two peripheral green squares (3.4° of visual angle each) located 16° to the left and right of the fixation point (duration 50 ms). The subjects were asked to react as quickly as possible to the presentation of one of the two visual targets by pressing a single button with the right thumb. The visual target might or might not be preceded by the cue, depending on the experimental conditions (Fig. 1). Stimuli were presented and behavioral data were acquired using a real-time acquisition system (ADwin-Pro, Keithley Instruments, Cleveland, OH) controlled by laboratory-made software (Docometre) by courtesy of Franck Buloup (Institut des Sciences du Mouvement, Marseille).

Pre-stimulus delays (time between the lightening of the central fixation point and stimulus presentation, i.e., the time during which proactive inhibitory control had to be sustained) varied from two to four seconds in steps of one second. In cue trials, Cue-Target Onset Asynchrony (CTOA) was manipulated so that the cue-target delay varied randomly across nine conditions: from 100 to 2100 ms by steps of 250 ms. Since a lengthening of the time necessary to release the inhibitory control after a cue has been presented can be expected as a possible effect of clonidine intake, CTOA duration was increased with respect to the landmark study [14] to maximize the chances of catching the complete dynamics of the process.

The control condition was performed in two separate blocks of trials composed of visual targets only. The uncertainty condition was performed in two other blocks of trials mixing cue- and no-cue trials.

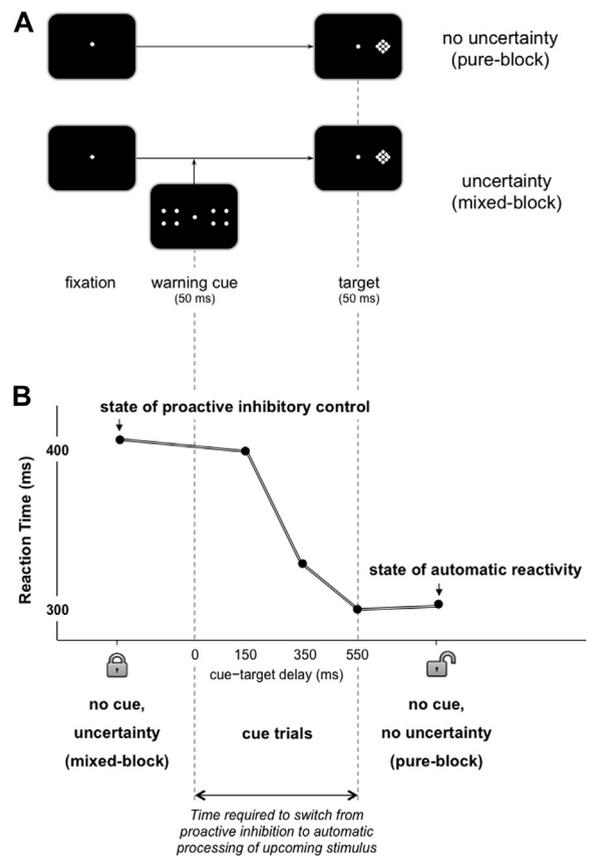


Figure 1. Principles and overview of the task design. (A) Experimental set-up used to assess proactive inhibitory control (cue-target detection task). (B) Behavioural markers of the dynamics of proactive inhibitory control in healthy subjects (mean age 57 years old; data taken from Ref. [14]). Proactive inhibitory control operates as a gating mechanism acting on movement initiation processes by anticipation of stimulus occurrence when the context is uncertain to prevent automatic responses to potentially inappropriate stimuli. 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 [29–31]. When there is no uncertainty about the upcoming stimulus, no proactive inhibitory control is required. Responses can be triggered automatically. This means that 1) the effect of a simple warning cue mainly consists in unbolting the gate before a target occurs, and 2) proactive inhibitory control can be easily assessed with appropriate cue-target reaction time tasks. Accordingly, no-cue trials in cue-target protocols show a dramatic increase in RT with respect to no-cue trials performed apart in pure-blocks. If a warning cue is presented sufficiently in advance of the target (long cue-target delays), 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 RT.

These four blocks were presented in a counterbalanced order for each condition of stimulation \times drug. Control blocks were composed of 48 trials each. Mixed blocks were composed of 96 trials each. Each subject performed 288 trials for each condition of stimulation \times drug, equal to 1152 trials in total. Subjects were instructed to comply with a maximum error rate of 10% on pain of being discarded from the analysis. When an overt response was given before target occurrence (false alarm), or no response was given within a one-second-time window (omission), the trial was aborted.

Drugs procedure

Clonidine was used to induce noradrenergic modulations (α 2-AR agonist). Specifically, clonidine is thought to decrease NA

release through presynaptic α 2-AR activation. Each patient was tested in four experimental sessions combining all conditions of stimulation (STN-DBS ON; STN-DBS OFF) and drug (Clonidine; Placebo). The first (S1) and the second (S2) sessions were separated by 24 h. The third (S3) and fourth (S4) sessions took place three months later, separated by 24 h. Since the long half-life of clonidine does not allow complete withdrawal from the body from one day to the next, patients always received placebo first (at S1 and S3), and then received a clonidine (at S2 and S4, 150 μ g oral dose), in a simple blind design. The drug was administered 90 min before testing to maximize the effect. Since clonidine has well-established anti-hypertensive properties, the blood pressure was monitored every 30 min from intake time to one hour after the experiment. The order of the ON and OFF conditions of STN-DBS was counter-balanced across participants (Fig. 2).

Statistical analyses

Reaction time

We first assessed the dynamics of release of inhibitory control after a cue had been presented within each experimental condition of Stimulation by Drug, by means of one-way analyses of variance (ANOVA) applied to mean RT data. No significant differences were observed between CTOA 600 and longer CTOAs for any experimental condition. Thus, these conditions were collapsed and referred to as “CTOA550+” for further RT analyses.

Then, for the sake of design optimization and clarity, statistical analyses were performed in successive steps by means of ANOVA applied to mean RTs (excluding RTs exceeding ± 3 standard deviations). First, the effect of STN-DBS was tested in the placebo condition in order to compare the present results with those of the reference study of Favre and colleagues [14]. A 2 STN-DBS (ON, OFF) \times 5 Trial (no-cue mixed-block, no-cue pure-block, CTOA100, CTOA350, CTOA550+) design was used. Second, the effect of the drug was tested in the OFF STN-DBS condition by means of a 2 Drug (Clonidine, Placebo) \times 5 Trial (no-cue mixed-block, no-cue

pure-block, CTOA100, CTOA350, CTOA550+) design. Third, the effect of the drug was tested in the ON STN-DBS condition by means of a 2 Drug (Clonidine, Placebo) \times 5 Trial (no-cue mixed-block, no-cue pure-block, CTOA100, CTOA350, CTOA550+) design. Post-hoc comparisons were performed when necessary using Newman–Keuls tests. All tests were two-sided and $P < 0.05$ was considered significant.

Response accuracy

Joint analyses were performed to assess the error rates. False alarms and abnormally short RTs (< 150 ms) were pooled together (anticipations). Omissions were considered separately. The percentages of anticipations and omissions were submitted to separate ANOVAs after ArcSine transforms. By contrast with RT analyses, CTOA does not represent a variable of interest and was not considered in error analyses. This reduction of the number of degrees of freedom allowed the setting-up of a unique statistical design in the form of a 2 Drug (Clonidine, Placebo) \times 2 STN-DBS (ON, OFF) \times 2 Condition (mixed-block, pure-block) ANOVA.

Results

Errors

On average, the global error rate was $5.3 \pm 7.5\%$.

Anticipations

A main effect of the trial ($F(1,15) = 81.53, P < 0.001$), not surprisingly, was that the rate of anticipations was higher in the mixed-block than in the pure-block condition (0.0027 vs. 0.0008). As has been abundantly reported previously, this effect is simply due to the fact that cue-induced automatic motor activations usually cause false alarms [32]. No significant effects of the drug or STN-DBS, nor any significant interaction, were observed.

Omissions

A main effect of the drug was observed ($F(1,15) = 11.56, P < 0.01$) revealing that clonidine broadly increases the number of omissions with respect to a placebo condition (0.0046 vs. 0.0031). A significant interaction of the drug with the trial ($F(1,15) = 5.9, P < 0.05$) specified, however, that this effect was mainly due to the increase of the rate of omissions in the pure-block condition (0.0044 vs. 0.0025 for the clonidine and placebo conditions, respectively, $P < 0.001$).

Reaction time

Effect of STN-DBS in the placebo condition

A main effect of STN-DBS ($F(1,15) = 7.84, P < 0.01$) was observed, revealing a broad RT decrease under STN stimulation (501.2 vs. 446.4 ms, for the OFF and ON STN-DBS conditions, respectively). The STN-DBS \times Trial interaction just failed to reach the conventional statistical threshold ($F(4,60) = 2.32, P = 0.067$). However, this trend yielded similar results to those previously reported [14]: a specific effect of STN-DBS was observed in the control condition (no-cue, pure-block). While PD patients are impaired OFF stimulation (RT are longer in this control condition than in the CTOA 550 + Trial: 488 vs. 429.5 ms, $P < 0.001$), STN-DBS restores a normal pattern of results by reducing RT in the no-cue pure-block trial (405.3 vs. 391 ms, $P = 0.21$) and wiping out the RT difference observed when OFF-DBS (Fig. 3).

Effect of clonidine in the OFF STN-DBS condition

A main effect of Trial ($F(4,56) = 38.99, P < 0.001$) revealing the typical OFF STN-DBS pattern such as i) the longest RT was observed for the no-cue mixed-block condition (553.5 ms), ii) RT decreased

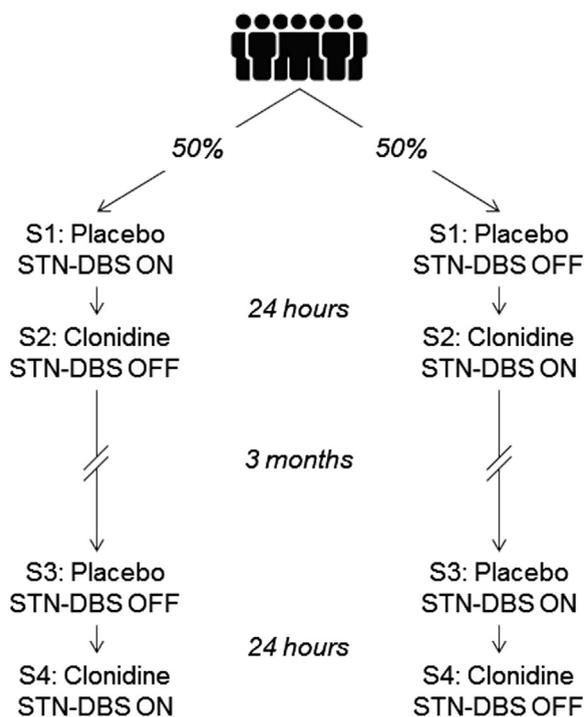


Figure 2. Overview of the study design.

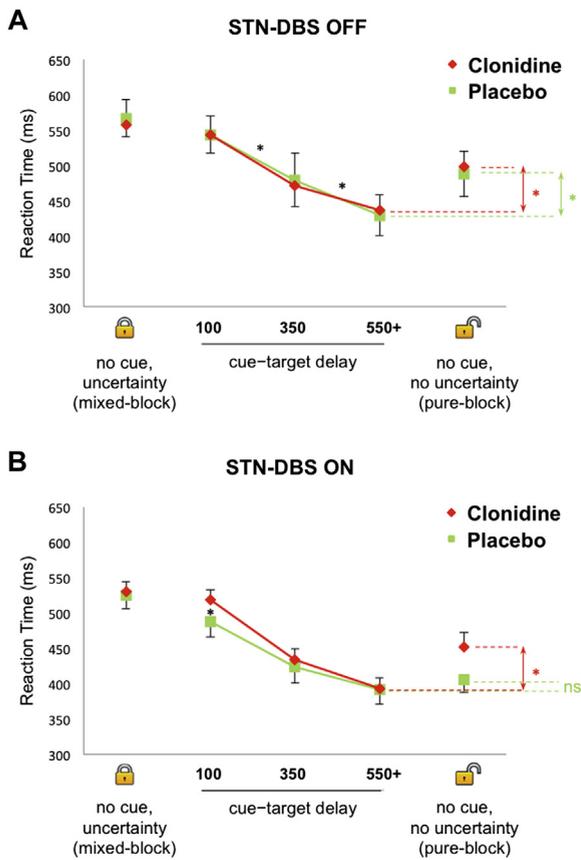


Figure 3. Respective effects of clonidine administration and STN-DBS on proactive inhibitory control impairment as assessed with reaction time.

as CTOA increased (535.3 vs. 462 vs. 424 ms for CTOA100, CTOA350 and CTOA550+, respectively, all P s < 0.001), but iii) RT was longer in the no-cue pure-block trial with respect to the CTOA550 + Trial (484.6 vs. 423.9 ms, P < 0.001). Clonidine intake did not have any effect in the OFF STN-DBS condition (Fig. 3A).

Effect of clonidine in the ON STN-DBS condition

A significant Trial \times Drug interaction ($F(4,60) = 4.99$, $P < 0.01$) revealed a specific effect of clonidine. With respect to placebo, clonidine increased RT in the CTOA100 and the no-cue pure-block trials only (519 vs. 487.9 ms, 452.3 vs. 405.3 ms, all P s < 0.001). However, in the placebo condition, RT was not different in the no-cue pure-block and the CTOA550 + conditions (405.3 vs. 391 ms, $P = 0.22$), while in the clonidine condition, RT was longer in the no-cue pure-block condition than in the CTOA550 + condition (452.3 vs. 393.2 ms, $P < 0.001$). In other words, the effect of clonidine can be summarized as a return to the abnormal pattern observed in the OFF STN-DBS state in the placebo condition (Fig. 3B).

Correlation analyses

Complementary analyses were performed in order to test a possible interaction between the two types of medication administered to the patients (the noradrenergic modulation by clonidine and the dopaminergic modulation by levodopa or similar medication). More precisely, we tested the hypothesis that the behavioral effect of clonidine observed in the no-cue pure-block in the ON STN-DBS condition could be related to the levodopa equivalent dose – LED. To this aim, we exploited the inter-individual variability of LED due to variable *time since surgery* across subjects (Table 1). We used as a behavioral index of the drug effect the mean individual

difference in the no-cue pure-block RT between the ON and the OFF STN-DBS states. This variable (Δ RT) was associated with the corresponding individual LED value. No significant correlation was found ($r^2 = 0.13$, $P = 0.17$).

Additionally, since *time since surgery* is a determinant factor of STN-DBS efficacy [33], we assessed a possible relationship with the effect of clonidine as revealed by our behavioral index (Δ RT). No significant correlation was found ($r^2 = 0.04$, $P = 0.45$).

Discussion

Here, we confirm the basic result of our previous work suggesting that: i) PD patients are impaired in their ability to switch from a proactive, inhibitory mode of control of movement initiation to a reactive, automatic mode of sensorimotor processing, ii) STN-DBS specifically acts by regaining control of the state of “self-initiated automaticity” when appropriate [14]. This was seen through i) an increase in RT in the OFF STN-DBS state specifically when the situation prompted to release control (no cue, no uncertainty, pure-block), and ii) the return to a normal pattern of RT in the ON STN-DBS state (Fig. 3). In other words, slowness in movement initiation in PD patients might partly be due to the fact that patients are locked into a mode of executive control maintaining inappropriate response inhibition. STN-DBS would restore the ability to voluntarily release the default, executive control mechanism which normally refrains from reacting in uncertain contexts.

There are substantial reasons to assume that STN activity is directly modulated by the NA system [19,20], but direct evidence from human studies is missing. There are several issues here, all of which are hotly discussed. First, a number of important questions about the basal ganglia (BG) circuitry remain unresolved, including the issue of the exact roles of the striatum and STN, the two input stations of the BG [34–37]. Second, identifying interactions between STN activity and the NA system might usefully inform the current debate on non-dopaminergic approaches to medical and surgical therapies [38–42].

Relevance to anatomo-functional models of motor control

Movement control heavily relies on the ability to suppress undesired or inappropriate motor activations. Importantly, inhibitory control not only accounts for the ability to counteract inappropriate actions, it also strongly accounts for the latency of initiation of appropriate movements [32].¹ This complex and multifaceted function is supported by parallel cortico-BG-thalamo-cortical circuits [50,51]. A refined model of the BG circuitry states that motor cortical signals are first transmitted through the cortico-STN-pallidal hyperdirect pathway, producing early excitation in the internal globus pallidus (GPi), and inhibiting inappropriate movements [52,53]. Then, signals through the cortico-striato-pallidal direct pathway are thought to induce inhibition in the GPi and release appropriate movements. Finally, the cortico-striato-pallido (external GP)-STN-pallidal indirect pathway is supposed to mediate late excitation in the GPi and stop movements. In

¹ Here, we did not find evidence for STN-DBS induced impulsivity. Yet, the effect is not automatic and the mechanisms of action that induce impulsive behaviors under STN-DBS still remain obscure [43]. Several reasons might explain this inconclusiveness. Given the multifaceted aspect of response inhibition [44], it is likely that the effect is conditioned upon several factors related to the characteristics of the experimental task (e.g., go/nogo or high conflict situations would favor the observation of impulsivity [45,46]), the characteristics of the patients (e.g., psychosocial factors such as male gender increase the risk of impulsivity [47,48]), or the characteristics of stimulation (e.g., stimulation of the ventral STN region would facilitate impulsivity [49]).

compliance with the dynamics inferred from this anatomo-functional model, most studies interested in response inhibition have focused on the cascade of events launched by cortical responses to the external stimuli subjects must refrain from reacting to. However, psychophysical and neuroimaging studies in healthy subjects strongly suggest that response inhibition processes might also implement action restraint in anticipation, before any stimulus is provided to the subject [29–31,54–57]. By setting up a method that makes it possible to isolate this function, the present study suggests that the STN probably plays a pivotal role: While performance is impaired in a pathological state, direct high-frequency stimulation provides specific beneficial effects. The precise mode of action of STN-DBS cannot be inferred from the present study. Theoretically, STN-DBS might disrupt both the indirect and hyper-direct pathways, with subsequent potential effects on both slow tonic and fast phasic brain activity. It is indeed equally possible that STN-DBS acts by restoring normal cortico-BG tonic activity in the executive and motor networks, or acts by facilitating specifically the phasic activity supporting switches from controlled to automatic sensorimotor processing. Consistent with this view, growing evidence demonstrates anticipatory changes in STN local field potential activity in humans [58–60]. The present data call for this issue to be assessed, with greater resources being brought to bear on the whole brain activity preceding (not only the brain activity induced by) external stimulation with respect to the contextual requirements for movement initiation control.

Noradrenergic modulation of STN activity and movement initiation control

Up to now, there has been no direct evidence of the role of the noradrenergic system in movement initiation control in humans. The present results reveal specific effects of clonidine on the ability to switch from controlled to automatic behavior. This effect was inferred from an increase in RT with respect to the placebo condition in the control trials in which patients were invited to voluntarily release proactive inhibition (Fig. 3B). This interpretation in terms of α 2-AR agonist-induced executive dysfunction is consistent with the observation that patients made more omissions (did not respond at all) under clonidine in this condition. A somewhat lower effect on RT was also observed in the CTOA100 condition (Fig. 3B), meaning that clonidine also delayed the cue-induced release of proactive inhibitory control. Taken together, these results suggest that the difficulties experienced by PD patients to voluntarily release the default mode of executive control that maintains action restraint could be related to the activity of the noradrenergic system. Following our initial suggestion about the non-motor and non-dopaminergic origin of akinesia [14,61], we now assume that troubles and slowness in movement initiation rely, at least partly, on the modulatory action of noradrenaline. In good agreement with this idea, Moreau and colleagues have also recently showed that NA system might be involved in the pathophysiology of gait disorders in PD, such as freezing of gait which can be viewed as a failure to initiate movement [23].

Traditionally, it is believed that the noradrenergic system plays a non-specific role in cognition as it is essentially involved in arousal, attention and vigilance [62–64]. This idea is still very influential [65]. Yet, it has been proposed – mainly on the basis of animal studies – that the noradrenergic system has a more subtle and specific function in the control of behavior. It is involved in the top-down control of task execution, and hence participates in the adaptive regulation of performance [66]. The results of the present study are consistent with this view, and further specify some of the mechanisms that might be involved in this broad function. Indeed, we did not find non-specific effects of clonidine, as predicted by

attentional accounts, but conversely we found highly specific effects of executive origin. By acting as a gating mechanism, whose function is to prevent responses in uncertain situations, proactive inhibitory control probably plays a pivotal role in behavioral control in general. In this respect, it is worthwhile recalling that previous behavioral and neuroimaging studies in healthy humans have suggested that most of the effects observed in experiments using classical cueing methods to probe attentional functions are in fact due to the executive mechanisms that are mandatory to refrain from reacting to cues. This reinterpretation especially concerns alertness [29,30] and visuospatial orientation [67], and raises the more general question of the integrative modeling of these intrinsically related psychological functions. Besides these conceptual issues, but consistent with our view, pharmacological manipulation studies (recently reviewed by Chamberlain and Robbins [68]) have demonstrated that the NA system exerts variable but profound influences on various cognitive functions, including attention, working memory, cognitive flexibility as well as response inhibition.

A second major finding of the present study is that clonidine was found to cancel the beneficial effect of STN-DBS (Fig. 3B). This suggests that the modulatory action of NA might be mediated by the STN. At least, a regulated activity of the STN (ON STN-DBS state) is a prerequisite for revealing the effect of clonidine (Fig. 3A vs. Fig. 3B).

NA has long been considered as having a minor influence on STN regulation [17,18]. However, recent reports have contradicted this view. Animal studies have demonstrated that STN neurons are under the control of α 1- and α 2-AR, further supporting the role of NA dysregulation in PD symptomatology. Notably, it has been shown that α 2-AR agonist induces an increase in the spontaneous activity of rats' STN neurons [19]. More recently, Delaville and colleagues [26] have demonstrated that NA depletion by DSP-4 induces profound behavioral (hypolocomotor activity) and electrophysiological (STN neurons discharging with a burst and irregular pattern) alterations in rats that resemble those observed in Parkinsonian patients [69,70]. Additional arguments are also provided by clinical studies. In PD patients provided with a β 1-AR antagonist during STN-DBS surgery, Coenen and colleagues [24] found a reduction of motor symptoms coupled to a suppression of STN spiking activity. Finally, combined together, recent neuroimaging studies assessing respectively the modulations of activity induced by STN-DBS in PD patients with PET [45], and the modulations of activity induced by clonidine in non-implanted patients and healthy controls with event-related functional MRI [71], provide indirect support for an interaction of the NA system and STN activity. Indeed, DBS and NA pharmacological manipulation were both found to induce activity changes in structures already known to be involved in proactive inhibitory control.² Interestingly, both the STN and the cortical structures mediating proactive control (such as the medial prefrontal cortex, the posterior cingulate cortex/precuneus and the pre-supplementary motor area) receive noradrenergic inputs [20,72,73]. All these elements strongly suggest a functional coupling between STN activity and the noradrenergic system. They demonstrate the anatomo-functional

² In controls, clonidine was found to increase brain activation in the medial parietofrontal network initially identified by Jaffard and colleagues [29,30]. The difficulties in movement initiation observed in PD were associated with activity changes in the posterior node of this network (mainly in the posterior cingulate cortex/precuneus), consistent with the dysfunctions of this region observed in cases of DBS-induced impulsivity [45]. Under clonidine, inappropriate implementation of inhibitory setting and consequent slowness in movement initiation were enhanced and more closely associated with modulation of the anterior node of the proactive control network (medial frontal cortex).

plausibility of our interpretation of the present behavioral results, namely that clonidine-induced activation of post-synaptic α 2-AR interferes with STN-DBS effects by switching STN activity back to a pathological pattern that induces executive deficits.

Relevance to non-dopaminergic approaches to medical and surgical therapies

The present results might open the way towards two different therapeutic perspectives. First, after surgery, PD patients under STN-DBS might develop impulsivity [46,47,74–77]. So far, management options are not entirely satisfactory as they mainly consist of reducing dopaminergic medications with the risk of developing the so-called dopamine agonist withdrawal syndrome [78–80]. The present results suggest that introducing α 2-AR agonist might be relevant for reducing this aversive effect. In the same vein, clonidine has recently been shown to induce inhibition of glutamate release onto the ventral tegmental area (VTA) [81], a brain structure central to reward processing and addiction, which is overdosed by dopamine-replacement levels that are therapeutic for motor symptoms in PD patients with impulse control disorders [48,82]. Finally, it is worth mentioning that clonidine is effective in reducing impulsivity in other pathological conditions. This is especially the case for attention-deficit/hyperactivity disorder [83], Tourette's syndrome [84], and tic disorders [85,86].

Second, given that clonidine, an α 2-AR agonist, induces specific executive deficits, it might be relevant to explore the effect of an α 2-AR antagonist in PD. Indeed, it is tempting to speculate on the basis of the present results that this kind of agent might conversely improve these specific executive functions. We obviously have in mind the potential benefit of a complementary α 2-AR antagonist medication on refractory symptoms such as akinesia. In fact, it has previously been shown that α 2-AR antagonists improve tremor and rigidity in the reserpinized rat [87], have a potent effect on levodopa-induced dyskinesia (LID) in a monkey model of PD [88,89], and can extend the anti-Parkinsonian effect of levodopa in MPTP-treated monkeys [90,91]. In PD patients, although conflicting results have been reported, preliminary clinical trials have suggested that this therapeutic approach reduces bradykinesia and rigidity [92] as well as LID when given in combination with levodopa [93]. In other terms, there is a broad spectrum of possible outcomes for this class of drugs, but its effects on movement initiation control have so far never been explored.

In light of the aforementioned studies, the importance of the possible interaction between noradrenergic and dopaminergic medications must be stressed out. Although our data did not provide direct evidence in favor of this hypothesis, the results of the correlation between the behavioral marker of the effect of clonidine and the LED neither allowed rejecting this possibility. It is clear, especially from the animal literature, that there is a cross-talk between the noradrenergic and dopaminergic systems [94]. For instance, NA activity from the LC might modulate dopamine (DA) neuronal activity in the VTA [95–97], as well as DA can influence the neuronal activity of LC-NA neurons since the LC is reciprocally innervated by the VTA [97,98]. Further studies are needed to address the issue of the mutual modulations of the noradrenergic and dopaminergic systems in humans, in relation with the acknowledged role of the latter in ICD [48,99,100]. In particular, a deeper understanding of the interplay between VTA, LC and the two input stations of the BG (Striatum and STN) may reveal a deeper insight into the possible combined influence of noradrenergic and dopaminergic medications on motor and inhibitory control.

In conclusion, we assume that clinical symptoms such as akinesic freezing (possibly linked to the inability to release proactive

inhibitory control) or impulsivity (possibly linked to the inability to implement proactive inhibitory control), which probably represent the opposite ends of the same continuum of executive dysfunction [14,45,101], might benefit from different medications targeting NA dysfunction [102]. Obviously, the present study only provides a proof-of-concept, and further pharmacological investigations are warranted to support this hypothesis.

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