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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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A B S T R A C T

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 (∝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 μg 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 neuropathophysiology 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 ∝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 Soletra, 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/µS/V)	RS (plot/Hz/µS/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.

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