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Research Report

Slowness in Movement Initiation is Associated with Proactive Inhibitory Network Dysfunction in Parkinson's Disease

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Abstract.

Background: Impairment in initiating movements in PD might be related to executive dysfunction associated with abnormal proactive inhibitory control, a pivotal mechanism consisting in gating movement initiation in uncertain contexts.

Objective: Testing this hypothesis on the basis of direct neural-based evidence.

Methods: Twelve PD patients on antiparkinsonian medication and fifteen matched healthy controls performed a simple reaction time task during event-related functional MRI scanning.

Results: For all subjects, the level of activation of SMA was found to predict RT on a trial-by-trial basis. The increase in movement initiation latency observed in PD patients with regard to controls was associated with pre-stimulus BOLD increases within several nodes of the proactive inhibitory network (caudate nucleus, precuneus, thalamus).

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Conclusions: These results provide physiological data consistent with impaired control of proactive inhibition over motor initiation in PD. Patients would be locked into a mode of control maintaining anticipated inhibition over willed movements even when the situation does not require action restraint. The functional and neurochemical bases of brain activity associated with executive settings need to be addressed thoroughly in future studies to better understand disabling symptoms that have few therapeutic options like akinesia.

Keywords: Response inhibition, fMRI, proactive control, reaction time, Parkinson's disease

INTRODUCTION

Slowness or failure in movement initiation in Parkinson's disease (PD) is particularly disabling and still poorly understood [1–3]. This aspect of akinesia [1] is classically associated with the cardinal motor features of the disease. However, it was recently suggested on the basis of behavioral and pharmacological studies that slowness in movement initiation might not be of purely motor nature. Indeed, dysfunction of the motor circuit and dopaminergic depletion only partly account for reaction time (RT) deficits in PD [4]. It has been suggested that difficulties in initiating movements in patients with respect to age-matched controls could rather have an executive origin [4–6]. These deficits could indeed be due to dysfunctions of unheralded mechanisms of inhibitory control of action.

Although it is widely accepted that response inhibition is globally impaired in PD [4, 5, 7–12], much more emphasis has been placed on the impairment of the *reactive* mechanisms that countermand an initiated action when instructed by a specific signal [8] than on *proactive* mechanisms that prepare a subject to refrain from reacting before he has been exposed to any stimulation [13–19]. This issue is important because these two modes of control involve partly distinct cortico-basal ganglia (BG) loops, and have different dynamics [13–19]. It thus requires specific methodological amendments to identify the behavioral and neural bases of proactive inhibitory control [17] and possible related dysfunctions in PD (Fig. 1). In addition, the two models do not make the same predictions regarding the clinical outcomes of inhibitory dysfunction. While purely reactive models predict impulsivity as the primary consequence of inhibitory control impairment, proactive models also predict difficulties in initiating movements [4]. As such, slowness in movement initiation could be due to the fact that PD patients are locked into a mode of control by which they maintain inappropriate response inhibition over willed movements even when the context does not require action restraint (Fig. 1). This hypothesis predicts overactivation during the pre-stimulus period in PD patients with respect to controls in the network

known to support this inhibitory function. However, there is currently no direct neural-based evidence supporting this theory. Here, we use event-related fMRI to assess the changes in pre-stimulus brain activity within the proactive inhibitory network that are associated with delayed movement initiation in PD.

MATERIAL AND METHODS

Participants

Two groups participated in the study. Twelve non-demented (MATTIS > 130), non- or slightly depressed (BDI < 13) parkinsonian patients, with no history of neurological disorder other than PD, were enrolled. Since dopaminergic medication was not found to improve proactive inhibitory control of movement initiation in PD [4], all patients were tested on regular parkinsonian medication. Fifteen matched healthy control participants, with no history of neurologic or psychiatric disorder, were also recruited. All participants were right handed with normal or corrected-to-normal vision. Demographic and clinical characteristics of the PD patients are presented in Table 1. The protocol was approved by the local Ethical Committee in Biomedical Research (N° CPP 11/094) and participant consent was obtained according to the code of ethics of the World Medical Association.

Experimental design and apparatus

Subjects were asked to react as fast as possible to visual go stimuli by pressing a nonmagnetic handgrip with the right hand (Fig. 1). 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. It served as a fixation point for the eyes. The target stimulus (go) was composed of eight other LEDs surrounding the central fixation point and forming a diamond (3.44° of visual angle). Stimuli were presented and behavioural data were acquired using a real-time acquisition system and the software Presentation™.

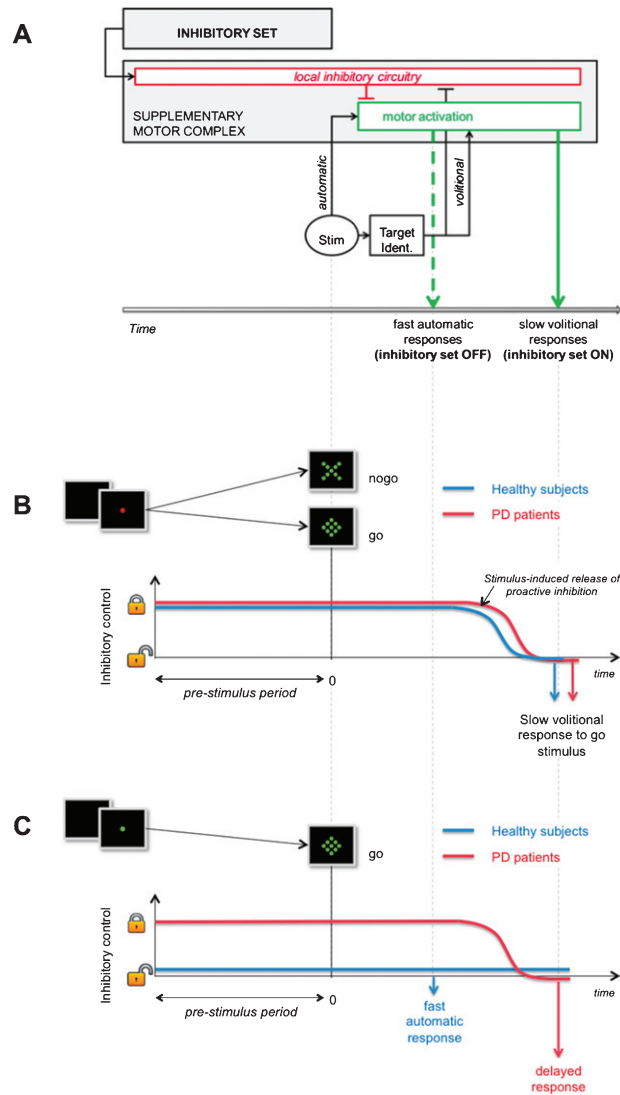


Fig. 1. *Psychological model, behavioural procedure, and clinical hypotheses.* A) Model of proactive control of response inhibition. The control of voluntary actions in stimulating environments directly relies on the ability to inhibit prepotent responses because any sensory stimulus may cause automatic motor activations that are likely to trigger fast but potentially inappropriate reflexive responses. When the situation is unpredictable, preventing automatic responses requires setting-up by anticipation the self-inhibitory circuitry of the SMC. When such proactive control is ON, automatic responses to any stimulus are inhibited. It is only when the stimulus is identified as a target-stimulus that inhibitory control is switched OFF, allowing production of slow volitional responses. By contrast, when the environment becomes predictable, the inhibitory set can be deactivated anticipatorily and temporarily. When proactive control is OFF, automatic responses are not inhibited and any stimulus might trigger fast automatic responses (see [51] for detailed description). Probing proactive response inhibition requires: 1- the use of a reaction time task successively performed with (B) and without (C) uncertainty about the upcoming stimuli, and 2- the analysis of pre-stimulus brain activity. B) When there is uncertainty about the upcoming stimulus, like in a go/nogo task (subjects must react to go but refrain from reacting to nogo-), proactive inhibitory control is required. Previous studies have shown that PD patients are not impaired with respect to controls, neither for implementing proactive control nor for releasing inhibition after a cue or a go signal has been presented [4, 6]. C) When there is no uncertainty about the upcoming stimulus, like in a simple target detection task, no proactive inhibitory control is required. Healthy subjects can trigger fast automatic responses. However, this is not the case for PD patients, who might be locked into an inappropriate mode of executive control leading to the implementation of proactive inhibition even when the situation does not require action restraint [4, 6]. The identification of the target stimulus (go) would act as an external cue to trigger the release of proactive inhibition, accounting for delayed response latency in PD [4, 6]. In other words, slowness in movement initiation in PD patients might be due to a dysfunction of the internal control of proactive inhibition release. In the present study, we focus on this simple experimental condition, the only one which is relevant to the issue of dysfunctional proactive control, and track the differences in pre-stimulus brain activity between PD patients and matched controls to test the physiological plausibility of this hypothesis.

Table 1
Demographic and clinical characteristics of the participants

	Healthy controls (<i>n</i> = 15)	PD patients (<i>n</i> = 12)	Group difference
Age in years (SD)	52.5 (11.2)	56.2 (8.9)	ns
Male/Female	6M/9F	8M/4F	ns
Unified Parkinson's Disease rating Scale-III		12.7 (4.8)	–
Disease duration in years (SD)		6.1 (2.3)	–
Levodopa Equivalent Dose (mg/day)		948 (320)	–

SD, standard deviation; ns, not significant; LED = Levodopa Equivalent Dose (calculated according to [21]). Two sample *t*-tests were used to compare demographic variables between groups.

The fixation point appeared at the beginning of a trial and lasted until the end of the trial. Prestimulus delays (time between the beginning of a trial and stimulus presentation) varied randomly from 2 to 6 seconds in steps of 1 sec to avoid predictability of stimulus occurrence. In order to optimize the discriminative power of the fMRI contrast vis-à-vis proactive control activation, we used only the longest prestimulus delays (4 to 6 seconds) [16]. The inter-trial interval varied randomly and exponentially from 2 to 6 seconds. The target was presented for 100 ms. Experimental data were composed of four runs of 20 trials randomly presented.

Force signals from the nonmagnetic handgrip were sampled at 1000 Hz (12 bits A/D converter) and filtered with a second-order Butterworth filter (30 Hz lowpass cut-off frequency with dual pass to remove phase shift). RTs were derived from classical time series analyses developed and described in more detail in previous studies [20]. Based on the distributions of baseline fluctuations and response peaks, movement initiation was defined as the moment in time at which the grip force exceeded the baseline mean force signal plus 35%, provided that the signal continuously increased till response peak force. RT was defined as the time between target presentation and movement initiation.

Images were acquired on a 1.5-T Siemens MRI scanner, equipped with a circular polarized head coil. For each participant, we acquired a high-resolution structural T1-weighted image (EPI sequence, resolution 1 × 1 × 1 mm) in sagittal orientation, covering the whole brain. For functional imaging, we used a T2*-weighted echoplanar sequence, covering the whole brain with 28 interleaved 3.44-mm-thick/0-mm-gap axial slices (repetition time = 2620 ms, echo

time = 60 ms, flip angle = 90°, field of view = 220 cm, 64 × 64 matrix of 3.44 × 3.44 × 4.4 mm voxels).

Data processing

We assessed RT and error rates (after ArcSin transform) differences between the two groups by means of Mann-Whitney U tests. Correlations were calculated between the experimental data (RT) and clinical data (UPDRS, akinesia score, MATTIS, BDI, disease duration, Levodopa Equivalent Daily Dose –LEDD, calculated according to [21]) in order to control for the effects of disease severity, clinical symptoms, and dopaminergic medication.

Neuroimaging data were processed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>), according to the general linear model. The first five functional volumes of each run were removed to account for magnetic saturation effects. The remaining 240 images were corrected for differences in slice acquisition time and realigned to correct for head movement. Outlier scans (>1.5% variation in global intensity or >0.5 mm/time repetition scan-to-scan motion) were detected and repaired using the ArtRepair SPM toolbox (<http://spnl.stanford.edu/tools/ArtRepair/ArtRepair.html>). Spatial normalization was improved using the DARTEL toolbox on an MNI template. Data were spatially smoothed with an isotropic Gaussian filter (8 mm full width at half maximum).

All events were time-locked to the onset of the cue, modeled according to their onset and their duration, and convolved with a canonical hemodynamic response function. We focused our analysis on the pre-stimulus period, all other events being considered as events of non interest in the statistical analysis. Since functional studies in healthy subjects have shown that proactive inhibition may elicit activity in the striatum, the subthalamic nucleus, the supplementary motor area (SMA), the dorsal premotor cortex (PMd), the angular gyrus, the dorsomedial prefrontal cortex, the thalamus, the insula and the right inferior frontal gyrus (rIFG) [13–15, 18, 19, 22–25], we used a mask encompassing only these regions, based on the aal atlas [26]. Data were high pass-filtered with a standard filter cutoff frequency of 128 s and summarized into one contrast per subject for which the signal intensity of the pre-stimulus period was contrasted to the baseline signal intensity in each voxel. The statistical parametric group maps were generated with a random-effects model. The individual statistical maps were entered into a two-sample *t*-test PD vs. controls.

In order to further assess the relationship between the level of pre-stimulus activity within the proactive network and the latency of movement initiation, we performed a complementary regression analysis. To better characterize the variability seen in behavior, we pooled the two groups and used individual normalized RT (RT/mean) as a parametric regressor of the pre-stimulus BOLD. The regressor effect was summarized into one contrast per subject. We applied a one sample *t*-test on the individual statistical maps. All maps were thresholded at $p < 0.001$ uncorrected for display purposes, and all results were reported after peak-level cluster-wise family wise error (FWE) correction for multiple comparisons.

RESULTS

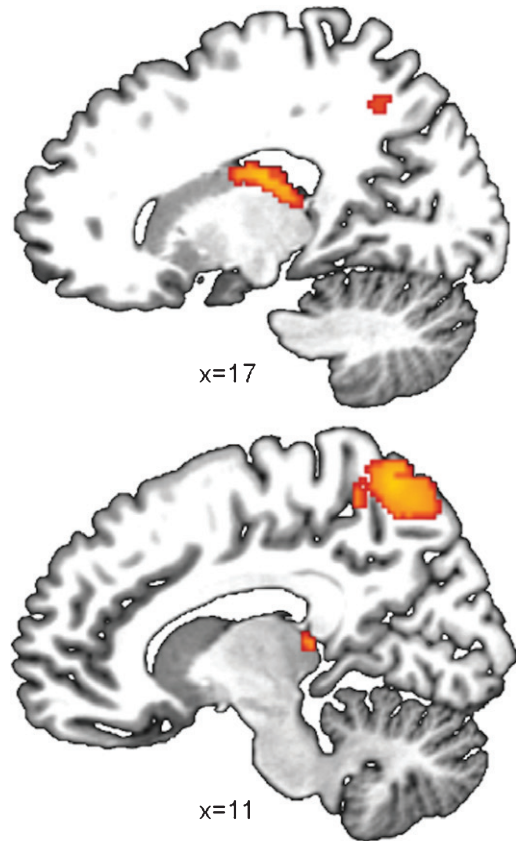
Behavioral data: No effect of Group was observed on the error rate ($2.3 \pm 5.8\%$, $p > 0.7$, all errors being due to premature responses to go trials). RT was significantly longer for PD patients than healthy controls (474 ± 91 vs. 400 ± 72 ms, $p < 0.05$). Changes in RT were not correlated with disease severity, LEDD or UPDRS score.

fMRI data: Several regions included in two different clusters showed greater BOLD signal in PD patients compared to matched controls: the precuneus (BA 7; $x: -16, y: -66, z: 60$; z -score: 4.91; cluster size: 1600; $pcor < 0.001$), and the caudate nucleus (body, $x: 20, y: -24, z: 16$; z -score: 3.87) extending to the thalamus (pulvinar, $x: 16, y: -16, z: 20$; z -score: 4.09) (a 134 voxels cluster which closely approached the conventional statistical threshold after conservative FWE correction; $pcor = 0.055$) (Fig. 2). The trial-by-trial regression analysis shows that the increase in RT correlates with an increase of BOLD signal in the SMA ($x: 8, y: 2, z: 60$; z -score: 4.85; cluster size: 382; $pcor < 0.01$). The cluster was found to overlap both pre-SMA and SMA-proper, yet revealing a larger involvement of pre-SMA (cluster extent in the Y direction: $[-8: 23]$; Fig. 2). BOLD changes were not correlated with disease severity, LEDD or UPDRS score.

DISCUSSION

Although it is one of the cardinal symptoms of PD, akinesia still needs a narrowed and consensual definition [1–5, 27], as this term often includes both bradykinesia (slowing of movement), hypokinesia (decreased amplitude of movement) and failure to

A- Between-group differences



B- RT regression analysis

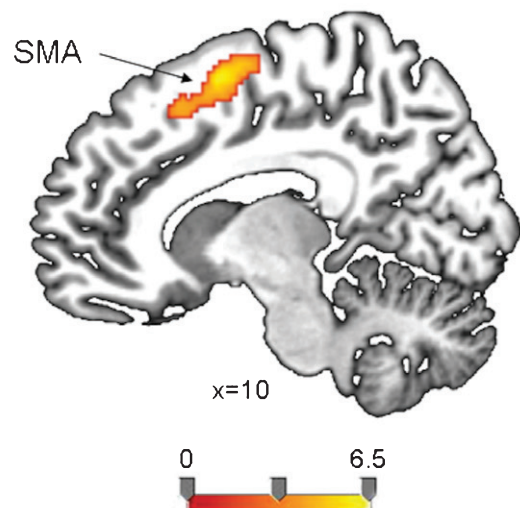


Fig. 2. fMRI results. A) Regions more activated in patients than controls during the pre-stimulus period. B) Region whose activity during the pre-stimulus period predicts RT.

initiate movement. Here, we focus only on movement initiation disorders. This aspect has certainly been overlooked in standard clinical assessments. At least, the lengthening of RT observed for PD patients in the present study does not correlate with the clinical scores.

The issue of inhibitory control dysfunctions in PD is a central matter for understanding motor and non-motor disorders [7–11, 28, 29]. Recent conceptual and methodological insights from healthy subjects have significantly challenged our understanding of response inhibition [17], and now offer the opportunity to test unexplored aspects of inhibitory control in PD [9]. In particular, proactive inhibitory control mechanisms have been revealed, that gate movement initiation in anticipation of external stimulation to prevent premature or erroneous responses to upcoming events when the context is uncertain [4, 14, 16]. Here, we report evidence that BOLD increase within the proactive inhibitory network during the pre-stimulus period predicts movement initiation lengthening. This was observed in the SMA (especially in the pre-SMA), within subjects on a trial-by-trial basis, regardless of medical condition. BOLD increase was also observed in the precuneus, the caudate nucleus and the thalamus in patients with respect to controls, accounting for movement initiation lengthening in the formers (Fig. 2). This result provides some further insights into how dysfunction of the thalamocortical route may produce disorders of movement initiation through its action upon cortical regions [27]. These observations raise more general questions about the segregation of the cortico-basal ganglia circuits into motor and non-motor domains. Indeed, there is some degree of integration and cross-talk across motor and associative (including executive) domains [3, 8]. One illustrative element is the involvement of the SMA in our main effect, which is known to support both motor and executive functions [30]. Our results also suggest that the cortico-striatal networks supporting the control of response inhibition might extend beyond the delimitation of the cortical territories described in the classical motor and associative circuits [3, 8]. This is especially the case of the precuneus, which was associated in the present study to the caudate, a pivotal node of the associative circuit. Although the links between BG and the prefrontal cortex in cognitive control have been extensively assessed, a possible role of the precuneus in executive control should not come as a surprise. Functionally, the precuneus is known to participate in executive functions through

its engagement under a variety of processing states [31]. Anatomically, the precuneus has strong interconnections with the striatum and the SMC [31]. Last, clinically, modulation of activity in the precuneus of PD patients is associated with disorders of response inhibition [5].

Broadly, the pattern of differential brain activity between patients and controls is consistent with the hypothesis that parkinsonian subjects maintain inappropriate inhibitory control although the situation does not require action restraint. Given that PD patients are not impaired in their ability to release proactive inhibitory control when externally triggered by a cue [4], the present results further support the view that the difficulty to initiate action is related to dysfunctional endogenous control of proactive inhibition.

Yet, it must be emphasized here that the exact role the different regions of the proactive network play in the control of movement initiation is still obscure [13, 14, 17]. Functions not directly related to the mechanism that actively suppresses the motor command are also involved. In particular, more general aspects of cognitive control may be engaged through, for instance, the proactive modulation of various processing states, of upstream perceptual processes, of temporal attention, of action monitoring, or even of response preparation itself [31–38]. In other words, since the brain structures showing abnormal proactive activity in PD patients were previously associated with these various functions, it is not possible to infer from the present results which processes among all of those involved in proactive inhibitory control actually account for movement initiation disorders. This further illustrates the complexity and functional multidimensionality of the cortico-basal ganglia circuits [8]. Now, two limitations of this study must be mentioned. First, the sample size may have been too small, and further larger studies are required to confirm the present results. Nonetheless, it is worth mentioning that all the results reported here survived a conservative statistical threshold (the FWE correction). Second, although the comparison is non-significant, the male:female ratio was reversed in the two groups with more females in the healthy control group. However, we are not aware of a possible gender effect in the functional anatomy of proactive inhibitory control.

Our findings might provide new lines of inquiry for future studies of movement initiation disorders in PD. First, further clarification of its pathophysiological and neurochemical features could rely on

the systematic analysis of the critical prestimulus brain activity related to response control. The non-dopaminergic origin of movement initiation disorders [4, 29], which is emphasized in the present results by the fact that neither BOLD modulations nor RT are related to the LEDD, calls for comprehensive pharmacological neuroimaging research targeting non-levodopa-responsive motor symptoms [6, 29, 39, 40]. This includes gait disorders, which might represent an extreme form of inhibitory dysfunction and associated disorders [41–47]. Second, akinetic symptoms, among which slowness in movement initiation, need to be considered along with other symptoms because they may not be the single outcome of proactive inhibitory control disorders. While impulsivity is usually viewed as the main consequence of disorders of response inhibition [28, 48], the present data show that dysfunctional inhibitory control may lead to a wider range of symptoms including difficulties in initiating actions. This proposal is consistent with other recent observations: first, hypoactivation within the proactive inhibitory network was found associated with impulsive action in PD [5, 49], and second, dopamine agonists were not found to modulate activity within the neural network underlying impulsive action (in contrast to the network underlying impulsive choices) [50]. Taken together, these arguments suggest that slowness in movement initiation and impulsivity might be the two sides of the same coin. Yet, further work is needed to identify more precisely the control mechanisms that are dysfunctional in PD.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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