Clinical Investigative Study

Functional Imaging of the Cerebellum and Basal Ganglia During Predictive Motor Timing in Early Parkinson's Disease

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ABSTRACT

BACKGROUND AND PURPOSE

The basal ganglia and the cerebellum have both emerged as important structures involved in the processing of temporal information.

METHODS

We examined the roles of the cerebellum and striatum in predictive motor timing during a target interception task in healthy individuals (HC group; $n = 21$) and in patients with early Parkinson's disease (early stage PD group; $n = 20$) using functional magnetic resonance imaging.

RESULTS

Despite having similar hit ratios, the PD failed more often than the HC to postpone their actions until the right moment and to adapt their behavior from one trial to the next. We found more activation in the right cerebellar lobule VI in HC than in early stage PD during successful trials. Successful trial-by-trial adjustments were associated with higher activity in the right putamen and lobule VI of the cerebellum in HC.

CONCLUSIONS

We conclude that both the cerebellum and striatum are involved in predictive motor timing tasks. The cerebellar activity is associated exclusively with the postponement of action until the right moment, whereas both the cerebellum and striatum are needed for successful adaptation of motor actions from one trial to the next. We found a general "hypoactivation" of basal ganglia and cerebellum in early stage PD relative to HC, indicating that even in early stages of the PD there could be functional perturbations in the motor system beyond striatum.

Keywords: Basal ganglia, cerebellum, fMRI, Parkinson's disease, prediction, timing.

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Introduction

Time, as the fourth dimension, is central to both perception and action. For instance, sensory events may have temporal lengths or they may define boundaries of "empty" temporal intervals. Likewise, moving targets possess temporal properties that need to be identified to assess their future trajectories. In action, timing is essential when producing sequences (ie, language) and when coordinating our movements with those of various moving objects in the external environment. Given this multifaceted manifestation of time, uncovering the neural substrate of timing prediction is not a trivial task. Over the years, the cerebellum, basal ganglia (BG), and other cortical areas (ie, prefrontal and parietal regions) have emerged as important structures dealing with various aspects of timing.[1-4] However, there are still debates in the literature about the primacy of each of these structures, as well as about their specific roles in timing and prediction.

Despite isolated studies disproving the role of the BG and cerebellum in timekeeping,[5,6] recent research provides increasing evidence for the involvement of both of these structures in the processing of temporal information.[7-10] Although both the BG and cerebellum were found to participate in time encoding,[11] most experiments showed that they played different roles, such as encoding short versus long time intervals,[12,13] dealing with explicit versus implicit timing,[14,15] or addressing timing versus temporal order.[16]

Many everyday skills, such as sports and the operation of motor vehicles or machinery, require precise timing.[17,18] Neurological disorders that disrupt motor timing lead to dysmetric or inaccurate movements.[19] Movements involve changes in muscle length over time, thus motor control and timing are inextricably related.[20] The cardinal clinical features of Parkinson's disease (PD) are tremor, hypokinesia, and rigidity, in other words, disorder of the movement. The degeneration is

present in the pars compacta substantia nigra with the depletion of dopamine. Evidence suggests that patients with PD suffer from marked deficits in motor timing within the milliseconds and seconds range.[21-23] These findings have indicated that the BG and their associated subcortical dopaminergic system play a crucial role in temporal processing, acting as a hypothetical "internal clock."[24] The role of dopamine in temporal processing and motor timing has been supported by the empirical data suggesting that dopaminergic medication improves timing problems in PD patients.[23,25] Studies with the simple motor tasks, investigating the neural activity related to bradykinesia, have found a similar pattern of striato-frontal underactivity in PD patients.[26,27] The group × task interaction showed that the bilateral cerebellar hemispheres and vermis, right thalamus, and left midbrain were more active in PD patients than controls during motor timing. Overactivation of the cerebellum has previously been described in PD patients during simple hand movements and has been interpreted as a switch to using alternative and intact motor pathways.[28,29] Of course, not all movements are timed by internal clock (which is used to time range of seconds-to-minutes, and it appeared to be linked to dopamine function in the BG).[24] Taken together, these studies suggest that there could be a functional complementarity in regards to the motor timing of the cerebellum and striatum, and that PD could be used as a "partial knockout" model to test the role of these two structures in motor timing.

Our previous behavioral study showed that unlike patients with cerebellar ataxia and essential tremor, patients with PD do not exhibit impaired motor timing during a task requiring mediated interception of a moving target.[30-32] This finding suggests that the cerebellum plays an essential role in this task. It is responsible for combined velocity perception, short interval timing, and error monitoring/error correction systems. Although the role played by the BG during an interception task may seem less dominant, its involvement cannot be completely excluded. The BG is necessary for the feedback-processing (reward learning) portion of the task, and thus it may be responsible for trial-to-trial action adaptation. It is known that an engagement of the ventral striatum during a reward or positive feedback is related to the phasic dopamine release.[33] The literature suggests that the dopamine system is the most involved in reward prediction and error processing.[34] In our task, the participants' knowledge that their actions produced a correct or an incorrect response could constitute the feedback, leading to further adjustments of the action, which in turn bears upon the correct prediction of the motor timing behavior.

In this neuroimaging study, we compared the brain activity of healthy participants with that of early PD patients engaged in the same motor timing task. Our hypotheses were built on several important recent findings. First, we considered evidence showing greater activation of striato-frontal areas (PET study) or enhanced functional connectivity between the cerebellum and putamen during motor timing in healthy participants.[23,35] Second, we built on a finding showing significantly greater activation of the cerebellum in the off-medication state in PD patients.[23] On the basis of this evidence, we expected to find differential activity in the two structures (BG and cerebellum) during the motor timing task. Specifically, we anticipated more activity in the BG observed in the healthy controls (HC) than in the early stage PD patients and different levels of activity in the cerebellum on the basis of possible compensatory neural circuits. We also expected a deficit in the feedback processing in the early onset PD patients to be shown in a trial-by-trial analysis (current vs. previous trials). A secondary objective of the study was to determine the possible side asymmetry of task-related brain activity in the BG among the early stage PD patients with lateralized symptomatology.

Methods

Subjects

Our study included 20 patients with idiopathic early-stage PD (PD group) and 21 healthy volunteers (HC group). The PD patients were scored according to the Unified Parkinson's Disease Rating Scale (UPDRS),[36] with a mean UPDRS score in the off state of 18.08, SD ± 3.8. The early stage PD group consisted of 11 men and 9 women, with a mean age of 55.4, SD ± 9.0 years; the average length of the medical condition was 2.5 years.

At the onset of illness, 6 patients had unilateral left parkinsonian tremor and 14 patients had unilateral tremor of right limbs. All PD patients had mild bradykinesia and hypokinesia. All PD patients received D2 agonists and none of them received L-DOPA medication (ropinirol five patients, mean dose 15.6 mg, SD ± 1.34; pramipexol seven patients, mean dose 2.3 mg, SD ± .31). Eight PD patients were drug-naive. The functional magnetic resonance imaging (fMRI) experiment took place in the off condition (off medication for at least 16 hours). PD group underwent battery of psychological testing; executive function was measured with the Tower of London test, no patient had a total correct standard score lower than 80, the cut-off score of borderline executive function impairment, and the Stroop test (none of the patients were in the impaired range). No participant scored lower than 27 on mini-mental state examination.

The control group consisted of 21 healthy volunteers with no symptoms of neurological diseases revealed by medical history (11 men and 10 women; mean age 57.0, SD ± 7.3). All subjects in both groups were right-handed according to the Edinburgh Handedness Inventory.[37] PD group nor HC group reported any visual problems. Standard neurological examination did not reveal any abnormalities related to the visual system abnormalities. All the subjects gave their informed consent before participating in the experiment. The study was approved by the Institutional Review Board of St. Anne's Hospital in Brno.

The Experimental Task

Before the experimental session, the task was carefully explained to the participants and practiced outside of the magnetic resonance scanner. We used an interception task that required both an accurate perception of target information and a precise predictive motor response. The task was identical to one used in the past in another study involving patients with cerebellar disorders.[30] Stimuli presentation was programmed using LabVIEW 6.1 (National Instruments, Austin, TX, USA). In each trial, the participants were asked to intercept a target that moved from the left to the right on a computer screen by pressing a button with the right finger. The target was a green

Table 1. Stimulus Characteristics

Movement Type	Speed	Target Angle 0°	15°	30°	Measurement Unit
Constant	Slow	8.74	8.97	9.84	cm/sec
	Medium	10.59	10.87	11.92	
	Fast	13.89	14.37	15.81	
Acceleration	Slow	3.18	3.24	3.54	cm/sec^2
	Medium	4.85	4.93	5.40	
	Fast	8.80	8.97	9.85	
Deceleration	Slow	3.08	3.15	3.39	cm/sec^2
	Medium	4.53	4.63	5.00	
	Fast	8.58	8.74	9.51	

Table 1 shows the stimulus characteristics and the actual speed when different combinations of stimulus characteristics were used. For instance, the target moving with constant fast speed at 30° angle had the speed of 15.81 cm/sec.

ball that moved across the screen, from left to right, at three different angles (straight across, 15° angle, or 30° angle), and three different speed rates: slow, medium, and fast. To intercept the target, the subjects pushed a button that controlled the firing of a blue cannon located on the lower right side of the screen. Once fired, a fireball traveled up from the cannon with a constant speed (20 cm/second) to intercept the moving target. The interception zone was always in the same position on the screen: close to the right upper side of the screen. If the subject successfully intercepted the target, both balls exploded in a short animation. If the subject failed to intercept the target, no explosion animation occurred. Trials were presented in blocks. In each block, the target could have one of three different types of movements: constant, decelerating, or accelerating; only the angle and the velocity varied within a block (for details, see Table 1). Although our task may seem complex and long, we believe that it required minimal motor responses (just a button push every 2.5–4.5 seconds) and that the patients did not have strong motor symptoms that could seriously impair them. Actually, the postexperimental interview with the participants revealed that patients and HC alike enjoyed the task very much and perceived it as a game, rather than as a boring or hard task. None of the participants reported that they were tired at the end of the experiment.

To discourage a response strategy on the basis of counting the seconds from the target's appearance on the screen until the push of the button, we asked subjects not to count the time elapsed (overtly or mentally) during the whole experiment. In addition, we employed a counterbalanced presentation of various types of stimuli within a block such as to minimize the repetition of the same type of stimuli in consecutive trials. In this case, even if subjects would try to use a mental counting strategy to respond to stimuli, the fact that one or more movement parameters (angle, speed, type of movement) changed from one trial to the next rendered such a strategy useless, given that the travel time varied from one stimulus to the next. The duration of each trial varied from 2.5 to 3.5 seconds according to the combination of movement type, velocity, and angle. For each stimulus presentation, the subjects were allowed only one attempt to press the fire button. The computer system did not respond to any other additional button presses until the next trial started. There were 250 ms between trials.

The Experimental Design

The entire paradigm consisted of two parts: a practice session (one block) and the main task (six blocks). Subjects were scanned while performing both sessions. The main task was divided into six blocks separated by 20-second break periods that involved no stimuli. One break period also preceded the first and followed the last block. Each block consisted of 54 stimuli (trials) with a total of 324 stimuli for the entire task. Each combination of angle, velocity, and movement type (27 in total) was presented 12 times during the entire run of the task. The order of presentation of movement types, which were constant within each block, was selected pseudo-randomly from six preprogrammed variants. The duration of the whole experiment was 60 minutes.

Scanning Parameters

The scanning session was performed at the radiology department of St. Anne's University Hospital, Brno, on a SIEMENS Symphony 1.5 T apparatus (scanner). A total of 580 T2-weighted EPI scans were acquired during the entire functional run (TR = 2300 ms, TE = 35 ms, FA = 90°, FOV = 220 × 180 mm, inplane voxel size = 3.44 × 3.44 mm, 28 axial slices, slice thickness 4.40 mm, no gap). Two more dummy scans were acquired before each run to allow the fMRI signal to reach a steady state. Before the functional run, an anatomical volume consisting of T1-weighted MPRAGE scans with high spatial resolution was also acquired (TR = 1700 ms, TE = 3.93 ms, TI = 1100 ms, inplane voxel size .96 × .96 mm, 160 sagittal slices, slice thickness 1.17 mm, matrix 256 × 256 × 160).

Preprocessing of the Imaging Data

Preprocessing and statistical analysis of brain images were performed using SPM5 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 7.5 (Mathworks Inc., Sherborn, MA, USA). Spatial preprocessing included realignment and adjustment for in-scanner head movement related effects, coregistration of functional and anatomical images, spatial normalization into the stereotactic Montreal Neurological Institute (MNI) space, and spatial smoothing using an isotropic Gaussian kernel of 8 mm full-width at half-maximum. In the time domain, the imaging data were filtered with a high pass filter with 1/512 seconds cut-off frequency. An autoregressive component of the first order was included in the subsequent statistical models to account for serial correlations in the data.[38] Finally, the data were scaled to an overall grand mean of 100. The extent of the movement did not differ among controls/tremor-dominant patients/and other patients in fMRI. But even if the tremor would have induced more movement artifacts, in the preprocessing of fMRI data we tried to account for these effects by taking into account the head movements in the scanner during spatial realignment of the MR functional volumes. These movements did not surpass 3 mm in each spatial direction or more than 3° of rotation around them.

Statistical Analysis of Behavioral Data

In each trial, we recorded the outcome as a hit or a miss. To be able to use parametric statistical techniques with this dichotomous data and to have a normal distribution for the hit ratio, we computed the percentage of hits for each subject and for each type of trial based on a combination of movement type, velocity, and angle (as the number of successful trials over the total number of trials of the same kind; a total of six discrete values per block, given that the movement type was constant within the blocks). We then considered the mean of these percentages, now normally distributed, in our analysis. A general linear model (GLM) was employed to assess the differences in hit ratio between the two groups, as well as the influence of the movement parameters (velocity, movement type, and angle) on subject performance. Further, each miss trial was classified as an early or late error depending on whether the "fire" button was pressed too early or too late to achieve a hit. A trial-by-trial analysis was later performed using the proportion of each type of outcome in the current trial and in the trial preceding it (hit, early error, or late error), and by employing nonparametric methods (eg, Chi-square) to assess the association between the outcome types in consecutive trials.

Statistical Analysis of Imaging Data

The main purpose for the statistical analysis of imaging data was to identify the activation pattern in the BG and cerebellum during successful motor timing. Further, we were interested in the differences in the activation of these regions between the two groups with respect to the accuracy of task execution and the trial-by-trial adjustment. The statistical analysis was done at two GLM levels as implemented at SPM5. At the first level, the individual design matrix for each subject included nine regressors of interest as the trials were categorized according to the result of an actual trial (either hit: successful interception of the moving target; early error: button pressed too prematurely to hit the target; or late error: button pressed too late to hit the target) and the result of a preceding trial. This yielded nine stimuli functions, which were then convolved with the canonical hemodynamic response function to form nine regressors of interest. Each stimulus onset was modeled at the moment of the target appearance at the left side of the screen. The stimulus ended with the appearance of the following trial.

A simple contrast map (map of parameter estimates) for each regressor of interest was created for each subject. This yielded nine contrast maps per subject. These maps of parameter estimates (a total of 369 maps, 9 maps from each of the 41 subjects) were then processed at a second level random effect analysis to allow for a population level inference. Here we used two specific ANOVA models using flexible factorial design in SPM5. Model I involved the *subject*, *group*, *actual result*, and *previous result* as independent factors. The design matrix included the main effect of each factor as well as the interaction between the factors *group* and *actual result*. This model was used for testing the intercondition differences, with a focus on responses to the actual trials. Given that the behavioral results showed that the two groups were different in terms of their early errors relative to hits, we decided to use the contrast between these two predictors for the main imaging results to assess the differences in the BOLD signal between the HC and early stage PD groups. Model II involved the *group*, *actual result*, and *previous result* as independent factors. As before, the design matrix included both the main effect of each factor and the interaction between the factors *group* and *previous result*. This model was used for testing the intracondition effects with a focus on the type of responses in the preceding trials. The contrast was set to test the differences between the HC group and PD group. We used a small volume correction method for the inference, as our hypothesis concerns only the cerebellum and BG. For this purpose, a mask was created using the WFU Pick atlas (ver. 2.3) and AAL atlas.[39-41] All presented results were significant at the statistical level of .05 family-wise error (FWE) corrected.[42]

Results

Behavioral Results

We used a GLM model with subjects as the random factor, and group, movement type, speed, and angle as fixed factors to assess the effect of these variables on the hit ratio. The results showed that the group was not significant as an independent factor, neither as a main effect ($F_{(1,39)} = .92$, $P = .34$, MSE = 1200.34) nor as part of any interaction with the other independent variables ($P > .05$). In Figure S1 (panel A) shows, the movement type (accelerating, decelerating, and constant) and speed (fast, medium, and slow) had a significant effect on the hit ratio, both as main effects ($F_{(2,78)} = 85.63$, $P < .001$, MSE = 311.65 for movement, and $F_{(2,78)} = 10.48$, $P < .001$, MSE = 500.28 for speed) and in interaction with one another ($F_{(2,78)} = 49.70$, $P < .001$, MSE = 223.75). However, these effects were similar in both the groups. These findings suggest that the hit ratio of both groups was similarly affected by the kinematic properties of the target.

Given that the two groups had similar hit ratios, we next checked to see if they differed in terms of the distribution of their early and late errors. To do so, we separately compared the distribution of hits and early errors, and that of hits and late errors between the two groups, using nonparametric measures. The Pearson's Chi-square ($df = 1$) test showed that there was a significant difference between the distributions of hits and early errors between the two groups ($\chi^2 = 19.20$, $P < .001$). There was no such difference in terms of the distributions of hits relative to late errors ($\chi^2 = .27$, $P = .601$). Given that this nonparametric measure tends to increase with the number of cases evaluated, we decided instead to rely on phi and Cramer's V coefficients, which also use chi-square, but account for the sample size at the same time. These measures, too, were consistent with the chi-square values and indicated that the two groups differed in terms of the distribution of early errors, but not late errors, relative to hits (Fig S1, panel B).

We employed the same nonparametric method to analyze the trial-by-trial adjustment by comparing the distribution of hits and errors (both early and late) in a trial as a function of the distribution of hits and errors in the previous trial (Fig S2). Pearson's Chi-square ($df = 4$) as well as the phi and Cramer's V coefficients showed that there was a significant interaction between the distribution of hits and errors in one trial and that

of the subsequent trial ($\chi^2 = 58.10$, $P < .001$). The analysis of the standardized residuals (the standardized difference between the observed value within a cell and the marginal distribution) showed that hits in the initial trials tended to be followed by hits in the subsequent trials, with a decrease in early errors and late errors, whereas the reverse effect was observed after a late error.

We then performed the same analysis separately for each group. The results of the phi and Cramer's V coefficients showed that in both groups there was a significant association between the distribution of hits and errors in the previous trial and that of the current trial ($P < .001$). However, the analysis of the standardized residuals showed that although for the hits and late errors in the previous trial the general results were replicated for each group, they were different for the early errors: the subjects in the control group increased the percentage of hits after an early error in the previous trial, whereas those in early stage PD group tended to make more early errors in the same situation. Furthermore, this difference between the groups with respect to the trial-by-trial adjustment was found when analyzing the distribution of hits and errors (early and late) in the current trial as a function of group, separately for each type of outcome in the previous trial (early error, hit, and late error). In this case, the distribution of outcome in the current trial was different between the two groups only after early errors and hits ($P < .001$ and $P < .05$, respectively), but was similar after a late error ($P = .20$).

Overall, the behavioral results showed that the two groups did not differ significantly in terms of the hit ratio, neither overall nor in relationship to the kinematic properties of the target. However, the distribution of early errors relative to hits was different, as was their ability to adjust from one trial to the next. Specifically, the trial-by-trial adjustment was different after early errors and hits, when the HC group tended to increase their hit ratio in the next trial more than the PD group. These findings indicate that the individuals in the early stage PD group had trouble postponing their action although anticipating the moving target and adapting from one trial to the next after these failures.

The early stage PD patients with dominant right-sided parkinsonian symptomatology scored a 43% hit rate. The early stage PD patients with left-sided parkinsonian symptomatology scored a 39% hit rate; however, the difference between these two subgroups was not significant ($P = .174$).

Imaging Results

The neural substrate underlying the performance in the current trial

Given that the behavioral results showed that the two groups were different in terms of their early errors relative to hits, we decided to use the contrast between these two predictors to assess the differences in the BOLD signal between the HC and early stage PD groups.

First, we analyzed the BOLD signal corresponding to the contrast between early errors relative to hits as described in the Methods section in both groups combined. We found increased activation during hits relative to early errors bilaterally in the BG (Fig 1A). The maximum activation was found in the left putamen (MNI coordinates: −15, +9, −9, maximum *t*-value: 6.83; and MNI coordinates: −30, −9, +6, maximum *t*-value: 6.7), in the right caudate head (MNI coordinates: +9, +12, −6, maximum *t*-value: 7.28), and in the right putamen (MNI coordinates: +27, −15, 0, maximum *t*-value: 6.28). We also observed increased activation in the cerebellum, with maximum activation in the posterior right cerebellum, in lobule VI (MNI coordinates: +33, −60, −18, maximum *t*-value: 10.78; Fig 1B), and in the posterior left cerebellum, in lobule VIIIA (MNI coordinates: +15, −69, −48, maximum *t*-value: 6.81) at the corrected threshold. Next, we searched for the differences in the BOLD response between the HC group and the early stage PD group using the same contrast. We found that the difference between the groups in the activity in the area of the BG was not statistically significant at the FWE $P < .05$ (Fig 1C). However, we found greater activity in the HC group in small region of the right hemisphere of cerebellum lobule VI in hit/early error contrast. This is depicted on Figure 1D. The threshold is set to T = 3 to show the cluster of group difference. The maximum of this cluster (MNI +21, −78, −18) reaches the significance level ($P < .05$ FWE). We did not find any areas of greater activations for the early stage PD group than HC group.

The trial-by-trial adjustment

The second level of analysis, using Model II (involving the *group*, *actual result*, and *previous result* as factors for testing the size of the difference between the groups in the trials following either a hit, early error, or late error in the preceding trial) yielded three important results (Fig 1E–G). First, in the trials following a hit in the preceding trial, we found no statistically significant difference. However, there was a marginally significant difference in the brain activity of a small cluster in the right putamen. This is depicted on the Figure 1E. The threshold is set to T = 3 to show the cluster of group difference.[43] The cluster maximum (MNI coordinates: +27, −6, −9) is just beneath the significance level ($P = .064$ FWE). Second, in the trials following an early error in the preceding trial, we found a statistically significant difference (increased activity in the HC group) in the areas of the right putamen and the right cerebellum, lobule VI. This is depicted in Figure 1F and G. The threshold is set to T = 3 to show the clusters of group difference. The clusters maxima (MNI coordinates: +27, −9, −9 for putamen, and +24, −75, −18 for right cerebellum) reach the significance level ($P < .05$ FWE).

Finally, in the trials following a late error in the preceding trial, we found no statistically significant difference.

Regarding possible asymmetry in the activity in the BG in the early stage PD group based on the different dominant parkinsonian symptomatology, we found no differences in the BOLD activity in the targeted areas between the patients with right and left parkinsonian symptomatology. Therefore, we cannot confirm a dominance of the left or right area of the BG in timing prediction.

Discussion

The BG and cerebellum are considered to play a role in motor timing tasks related to prediction.[13,32,44,45] Recent

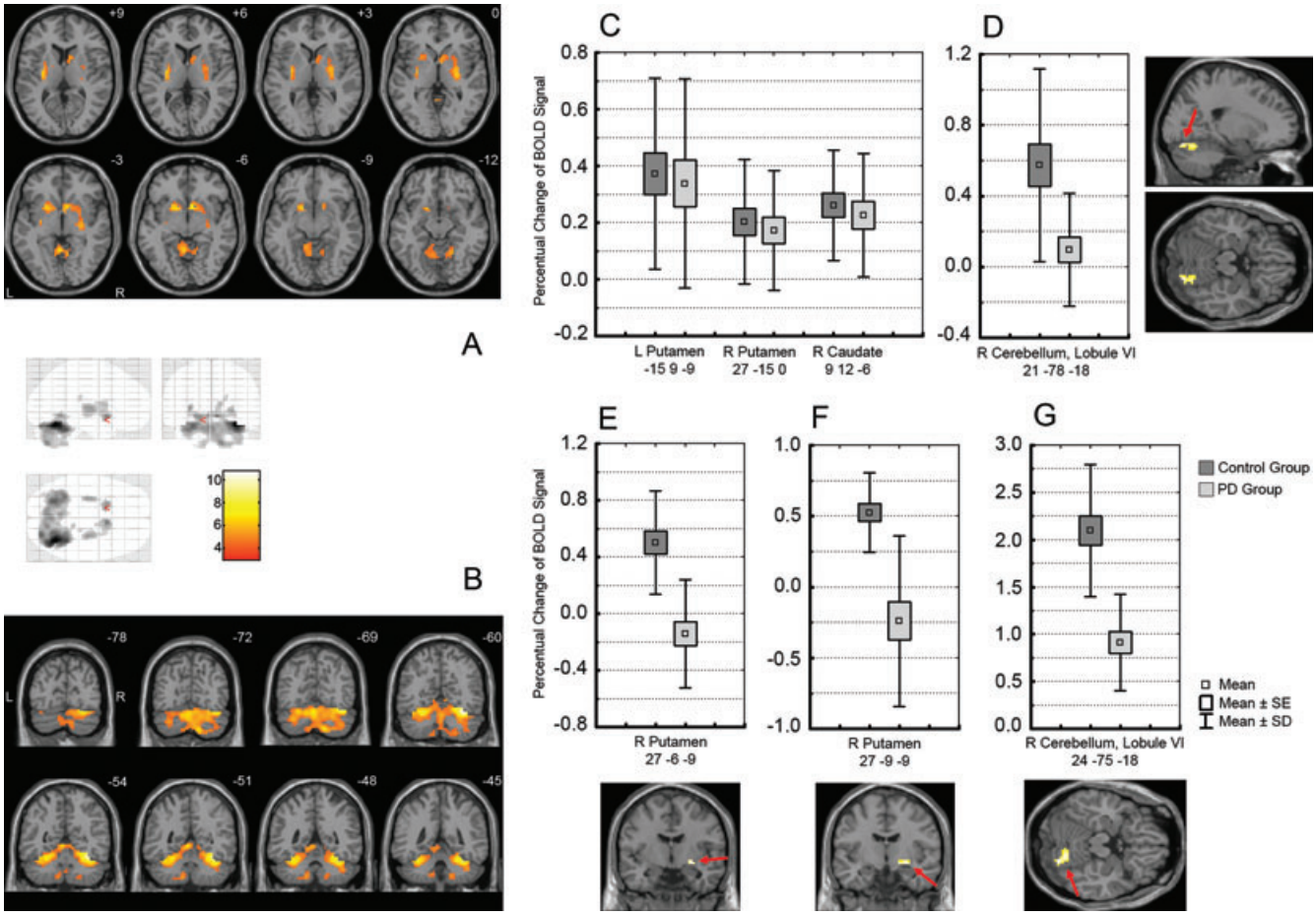

Fig 1. Functional scans showing increased BOLD signal in the HC group and early stage PD group when comparing hits and early errors. Cluster extent threshold = 5 vox, height threshold $P < .05$ FWE, small volume correction. (A) The region of the basal ganglia with the maximum activity in MNI coordinates: –15, +9, –9 (left putamen), +9, +12, –6 (right caudate head), and +27, +15, 0 (right putamen). The numbers indicate the position in mm on the z-axis above (+) or below (–) the AC-PC line; L = left; R = right; (B) the region of the cerebellum with the maximum activity in MNI coordinates: +33, –60, –18 (in lobule VI), and 15, –69, –48 (lobule VIII A). The numbers indicate the position in mm on the y-axis in front (+) or behind (–) the AC-PC line; L = left; R = right. The color bar represents *t*-scores. Based on Model I. (C) The percentage change of BOLD signal between hits and early errors, in the HC group and the early stage PD group in the areas of basal ganglia (left and right putamen). Separately for right and left side (MNI coordinates: –15, +9, –9 for the left putamen, MNI coordinates: +9, +12, –6 for the right caudate head, and MNI coordinates: +27, –15, 0 for the right putamen). The difference between the two groups in activation in the displayed areas is not significant. (D) Significant difference in the activation in the right cerebellum, lobule VI, between the HC group and the early stage PD group, contrast hits minus early errors, thresholded at T = 3 (cluster maximum at MNI coordinates: +21, –78, –18, $P < .05$ FWE, small volume correction). (C) and (D) Based on Model I, involving the subject, group, actual result, and previous result as factors for testing the intercondition differences with a focus on responses to the actual trials. (E), (F), and (G) Significant differences in activation between the HC group and the early stage PD group. Based on Model II, involving the group, actual result, and previous result as factors for testing the size of the intergroup difference in the responses following either a hit, early error, or late error in the preceding trial. The maps are thresholded at T = 3. (E) The difference in the response to hits in the preceding trial in the right putamen (cluster maximum at MNI coordinates: +27, –6, –9, $P < .064$ FWE, small volume correction). (F) The difference in the response to early errors in the preceding trial in the right putamen (cluster maximum at MNI coordinates: +27, –9, –9, $P < .05$ FWE, small volume correction). (G) The difference in the response to early errors in the preceding trial in the right cerebellum, lobule VI (cluster maximum at MNI coordinates: +24, –75, –18, $P < .05$ FWE, small volume correction).

meta-analyses revealed dissociable neural networks for processing duration with motor or perceptual components. An automatic timing system that works in the millisecond range and is used in discrete-event timing uses the cerebellum. The BG and related cortical structures are involved in a continuous event, cognitively controlled timing system that works in the second range and requires attention.[46,47]

Overall, our behavioral findings reveal that patients with early stage PD, off medication, display a preserved ability to reproduce a timing prediction task. Although the PD group was as successful in the motor timing task as the HC group, they had trouble postponing their motor actions until the proper moment (the early stage PD group made statistically more early errors). Even more striking was the difference in the trial-by-trial adjustment, where the PD group failed to adapt their behavior significantly more frequently than the HC group (after early errors and hits, the HC group tended to increase their hit ratio in the next trial to a greater degree than the PD group).

The imaging data support evidence indicating that the BG (the maximum activation was found in the putamen bilaterally,

right caudate) and cerebellum (the maximum activation was found in right lobules VI and VIIIA) both play a role in motor timing tasks (based on the results of both groups combined). Although the BG were activated in both the groups, no significant differences were found in BOLD signal. However, the cerebellum was found to be involved in correct predictions about the kinematic properties of the target, as well as in the postponement of the motor action until the proper moment (indicated by the significant increase of activity in lobule VI of the right hemisphere of the cerebellum in the HC group). This result is consistent with evidence indicating the involvement of both the cerebellum and BG in the accurate perception of events and precise prediction of motor responses. Furthermore, the results are consistent with behavioral findings showing that the early stage PD group committed significantly more early errors than the HC group.

Except for the described between-group differences, our study did not confirm our hypothesis and thus did not support the previous data, which showed that PD (ie, the nigrostriatal dopaminergic projection degeneration) disrupts interval timing.[13,23,48,49] Neither the supposed increased activity in the cerebellum nor the assumed alternative motor pathways in PD patients were confirmed.

There are several possible explanations for why our early stage PD group was as successful in performing the timing prediction task as the HC group. One is related to the early stage of the PD (mean UPDRS motor score in off state 18.08). As the impairment of the BG in the early stages of the PD is minimal, no significant decline of the overall time prediction function was observed. Also, minimal parkinsonian symptom deterioration was detected in the off-medication trial (applied 16 hours before the fMRI). But this explanation regarding the early stage of PD seems unlikely because the biochemical pathology at striatal level is already substantial by the time the patients start to show symptoms and signs. More than half of the individuals in the PD group were tremor dominant and no patient was markedly rigid in the off-medication state, which could explain the absence of an increased number of late errors. Instead, a significantly greater amount of early errors were made by the PD group, probably because of difficulty postponing the action until the proper moment. This indicates that although the general time prediction function may be preserved in this clinical population, the ability to link it with overt actions or behavior is nevertheless impaired. Thus, we believe that our results are significant given that we showed that even early PD patients, relative to HC, employ different motor timing strategies, and these are the result of a "hypoactivation" in cerebellum and striatum. The neuronal network underlying the tremor might not primarily reside in the BG. This possibility is supported by the strong correlation between thalamus (Vim), cerebellar activation, and tremor, as well as by the exquisite sensitivity of Vim manipulations to the cessation of tremor [50] and other groups. The relatively modest effect of levodopa treatment on the tremor, compared to its effect on hypokinesia and rigidity, indicates that nondopaminergic systems must also be involved in the development of the resting tremor. There is an assumption that the cerebello-thalamic and rubro-olivary projections are also involved in this process. However, the specific pattern of neurodegeneration accounting for the tremor in the akinetic-rigid forms of PD has not yet been found.

Our previous behavioral study showed that patients with cerebellar ataxia have marked deficit in motor timing, and confirmed that the cerebellum plays an essential role in this task.[30] Similarly, the fMRI results show an increased activation in the cerebellum in both the examined groups. In addition, all of our studied early stage PD patients had also mild bradykinesia and hypokinesia. For a more definitive conclusion, it is important that patients with the tremor-dominant versus akinetic-rigid forms of PD are examined separately. This may be an interesting and valuable subject for further research.

When we considered the trial-by-trial adaptation in the motor timing task, we found an increased BOLD signal change in the right putamen in the HC group compared to the early stage PD group when previous trials were hits or early errors. In contrast, a similar BOLD signal change was observed in the right cerebellum, lobule VI, only when the previous trial was an early error.

Our results imply that although the cerebellum is involved in dynamic adaptation to the task (and probably in prediction, as well),[51,52] the BG (putamen) is involved in reward or positive feedback, because it is activated after hits, as well. The BG propagates a successful signal in a kind of feedforward model for the future actions. Empirical literature shows that the striatum becomes activated when positive feedback occurs.[53-55]

The second goal of our study was to find a possible asymmetry in the BG activity in the PD group. We observed no effect of lateralization of PD symptomatology on the behavioral or imaging data. It can be concluded that the asymmetry of motor symptomatology, or generally the motor deficit in our PD group does not influence the results of the time prediction. Therefore, the difference in activity between the right and left sides of the BG was nonsignificant. Taken together, we did not confirm the dominance of the left or the right area of the BG in motor timing prediction.

We see the novelty of our findings in the recognition of distinct role of BG and the cerebellum in the predictive motor timing: current view is that the neural mechanisms involved in motor timing are mainly subcortical–the cerebellum and BG in particular,[12,20,56] but there is a debate as to the relative role played by these structures. Our suggestion is that cerebellum is associated exclusively with the postponement of action until the right moment, whereas both the cerebellum and striatum are needed for successful adaptation of motor actions from one trial to the next. We are aware of studies by Beudel et al[7] who recently tried to link the perception of time and spatial information using spatial and temporal anticipation of the movement. They found impaired velocity estimation in PD subjects whereas temporal prediction was selectively impaired in cerebellar subjects.[7] The authors further proposed the concept of space-referenced time processing and a clock-like processing model.[8] The subjects in these studies were asked to predict trajectories and spatial location, not to time the motor response on the basis of these predictions, as in our task, so they were not addressing the issue of motor timing itself, but rather the issue of timing and space.

Further research leading to the delineation of other brain areas active during this behavior in addition to computer-based neuro-rehabilitation programs could improve the cerebellar and PD patient performance, and decrease their degree of disability.[31] The influence of the nature of a task on performance and the task-specificity of deficits in temporal processing in PD subjects has been recently published.[22] Our behavioral results indicated that early stage PD patients used a different strategy than HC in this motor timing task as they were unable to postpone the initiation of their response and failed to adapt their behavior from one trial to the next. This difference in strategy is accompanied by a "hypoactivation" in PD patients relative to controls in cerebellum and striatum.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Fig S1. Panel A shows the movement type (constant, accelerating, and decelerating) and the speed (fast, medium, and slow), which both have a significant effect on the hit ratio, both as main effects for movement and in interaction with each other. Panel B shows the differences between the two groups in terms of the distribution of early errors, late errors, and hits. They differed in the distribution of early but not late errors relative to hits.

Fig S2. Analysis of the trial-by-trial adjustment by comparing the distribution of hits, early errors, and late errors in the current trial as a function of the distribution of hits and errors in the previous trial between early stage PD patients and HC volunteers.