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On-line motor control in patients with Parkinson's disease

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Summary

Recent models based, in part on a study of Huntington's disease, suggest that the basal ganglia are involved in on-line movement guidance. Two experiments were conducted to investigate this idea. First, we studied advanced Parkinson's disease patients performing a reaching task known to depend on on-line guidance. The task was to 'look and point' in the dark at visual targets displayed in the peripheral visual field. In some trials, the target location was slightly modified during saccadic gaze displacement (when vision is suppressed). In both patient and control groups, the target jump induced a gradual modification of the movement which diverged smoothly from its original path to reach the new target location. No deficit was found in the patients, except for an increased latency to respond to the target jump (Parkinson's disease: 243 ms; controls: 166 ms). A computational simulation indicated that this response slowing was likely to be a by-product of bradykinesia. The unexpected inconsistency between this result and previous reports was investigated in a second experiment. We hypothesized that the relevant factor was the characteristics of the corrections to be performed. To test this prediction, we investigated a task requiring corrections of the same type as investigated in Huntington's disease, namely large, consciously detected errors induced by large target jumps at hand movement onset. In contrast with the smooth adjustments observed in the first experiment, the subjects responded to the target jump by generating a discrete corrective sub-movement. While this iterative response was relatively rapid in the control subjects (220 ms), Parkinson's disease patients exhibited either dramatically late (>730 ms) or totally absent on-line corrections. When on-line corrections were absent, the initial motor response was completed before a second corrective response was initiated (the latency of the corrective response was the same as the latency of the initial response). Considered together, these results suggest that basal ganglia dependent circuits are not critical for feedback loops involving a smooth modulation of the ongoing command. These circuits may rather contribute to the generation of discrete corrective sub-movements. This deficit is in line with the general impairment of sequential and simultaneous actions in patients with basal ganglia disorders.

Keywords: basal ganglia; Parkinson's disease; on-line movement control; Huntington's disease

Abbreviations: EOG = electro-oculography; LED = light emitting diode; MD = movement duration; MRT = motor reaction time; PL = path linearity; PV = peak velocity; RT = reaction time; TC = time constant; UPDRS = Unified Parkinson's Disease Rating Score.

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Introduction

Initial studies investigating the neural substrates of on-line motor control have emphasized the critical contribution of two cerebral areas, namely the posterior parietal cortex in the region of the intraparietal sulcus and the anterior parasagittal cortex of the cerebellum (Desmurget *et al*., 2001; Desmurget and Grafton, 2003; Blakemore and Sirigu, 2003). More recent observations have also stressed the potential contribution of subcortical structures (Day and Brown, 2001) including the superior colliculus (Stuphorn *et al*., 1999, 2000; Sabes, 2000), and the basal ganglia. For the latter structure, the most convincing evidence came from a study by Smith *et al*. (2000) showing that patients with Huntington's disease

were greatly impaired at correcting both self-generated errors in movement trajectory and externally generated errors arising from the application of a force pulse at the beginning of the movement. To account for these observations, it was suggested that basal ganglia could be involved in on-line movement guidance and, more generally, in the process of forward modelling. This latter idea was based on computational and behavioural observations suggesting that feedback mechanisms rely on a 'forward model' that combines both efferent and afferent signals to estimate the location of the moving hand without delays (Gerdes and Happee, 1994; Wolpert and Miall, 1996; Bhushan and Shadmehr, 1999; Desmurget and Grafton, 2000; Ariff *et al*., 2002). Consistent with the involvement of basal ganglia in forward modelling, Lawrence (2000) recently presented a large set of convergent observations showing that basal ganglia dysfunctions affect the processes of motor prediction and error detection in various domains related to action, cognition and emotion (see also Schultz and Dickinson, 2000).

Although substantial, the evidence for specific basal ganglia involvement in on-line movement guidance and forward modelling is not totally compelling. Three reservations seem especially significant. First, a general predictive capability (i.e. for reward prediction or error detection during cognitive tasks) may be very different from the predictive process engaged in on-line motor control. Secondly, it has been repeatedly shown that Parkinson's disease patients can successfully use visual feedback to control reaching (Flowers, 1976; Flash *et al*., 1992; Ghilardi *et al*., 2000) and tracking movements (Bloxham *et al*., 1984; Day *et al*., 1984; Liu *et al*., 1999). Theoretically, a deficit in on-line movement guidance and/or forward modelling should result in a dramatic inability to track a target and/or correct the ongoing trajectory using visual feedback (Miall *et al*., 1993; Desmurget and Grafton, 2003). Thirdly, with respect to the study by Smith and colleagues (Smith *et al*., 2000), Huntington's disease does not affect the basal ganglia network alone. This disease involves substantial anatomo-functional abnormalities in other cortical and subcortical structures, even at the preliminary stages of the disease (Penney and Young, 1998). These secondary abnormalities might theoretically explain the inability of Huntington's disease patients to correct their ongoing movement. In addition, feedback control may be impaired only in Huntington's disease due to selective involvement of critical striatal elements, i.e. cholinergic intrinsic and gabaergic output neurons (Penney and Young, 1998).

The aim of the present study is to address some of these concerns by investigating the process of on-line motor correction in advanced Parkinson's disease patients. In these patients, functioning of the whole basal ganglia network is strongly impaired due to the degeneration of dopaminergic neurons of the substantia nigra pars compacta. We reasoned that if basal ganglia dependent circuits are critical for the process of movement guidance and more generally for the process of forward modelling, Parkinson's disease patients should exhibit the same inability as Huntington's disease patients to correct their ongoing trajectory when it happens to be erroneous. This hypothesis was tested in two successive experiments.

In the first experiment, we investigated the ability of advanced Parkinson's disease patients to amend the ongoing movement in response to a small subliminal target jump. In this task, often referred to as 'the double-step paradigm', the subjects are required to 'look and point' with their right unseen hand to visual targets presented in the peripheral visual field. In some trials, the target location remains stationary while, in others, it changes during the course of the ocular saccade. From a functional point of view, the movements directed at stationary and jumping targets have been shown to be identical when performed by healthy subjects (Desmurget and Grafton, 2000, 2003). This similarity takes root in the organization of the motor system. Indeed, when a subject is required to point 'quickly and accurately' at a stationary target located in the peripheral visual field, muscle activation starts nearly simultaneously for eyes and arm (Biguer *et al*., 1982; Gribble *et al*., 2002), indicating that the motor command initially sent to the upper limb is based on the initial peripheral visual signal. As reported in several studies, this signal is not entirely accurate (Prablanc *et al*., 1979; Bock, 1993). At the end of the ocular saccade, which roughly corresponds to hand movement onset (Prablanc and Martin, 1992; Desmurget *et al*., 2001), the target location is recomputed on the basis of peri-foveal information. The updated visual signal is then used by the nervous system to adjust the ongoing trajectory (Prablanc *et al*., 1986). Subliminal double-step experiments take advantage of this organization to increase the initial motor error without modifying the functional properties of the system (Desmurget and Grafton, 2000, 2003).

Results of the first experiment were inconsistent with previous reports suggesting that the basal ganglia mediate movement guidance (Smith *et al*., 2000; Lawrence *et al*., 2000). The second experiment was carried out to examine the origin of the inconsistency. We hypothesized that the difference in experimental designs was the critical factor. We thus investigated a task requiring corrections of the same type as those previously investigated in Huntington's disease patients, namely large consciously detected errors induced by large target jumps at hand movement onset. A potential theoretical substrate for the hypothesis that different experimental designs might lead to different observations lies in behavioural results, suggesting that different strategies might be used to correct different types of errors (Desmurget and Prablanc, 1997; Prablanc *et al*., 2003). Small subliminal errors might be corrected through a subtle modulation of the ongoing motor command (Desmurget and Grafton, 2003; Prablanc *et al*., 2003), whereas large consciously detected errors might be corrected through the generation of a discrete sub-movement (Van Sonderen *et al*., 1990; Flash and Henis, 1991; Paulignan *et al*., 1991).

Methods

Subjects

The subjects were enrolled after their informed consent was obtained. Control subjects were recruited in the Department of Neurology of the

Wertheimer Neurologic Hospital, among the persons visisting their hospitalized relatives. They were all right-handed and the experimental procedure was approved by the Human Investigations Committee of the Wertheimer Neurologic Hospital. Neither the parkinsonian nor the control subjects presented evidence of dementia or other neurological disorders at enrolment. The patients involved in this study were at a severe stage of disease and were under consideration for surgical treatment. They did not exhibit major signs of tremor. At the time of evaluation, they had been off medication for >12 consecutive hours (patients were tested in the morning, having been off medication since the previous evening). For each patient, the Hoehn and Yahr score and the Unified Parkinson's Disease Rating Scale (UPDRS) were determined before the experiment. Seven patients (four females and three males; age: mean 56 ± 11 years) and seven control subjects (three females and four males; age: mean 53 ± 7 years) took part in the first study. Five patients (three females and two males; age: 46 ± 8 years) and five control subjects (three females and two males; age: 55 ± 10 years) took part in the second study. The age difference observed between the two groups in experiments 1 and 2 was not statistically significant ($t < 1.5$; $P > 0.15$). Table 1 summarizes the clinical features of the patients for experiments 1 and 2.

Apparatus

The experimental device is illustrated in Fig. 1. It consisted of a horizontal table in front of which the subject was seated comfortably. The height of the table was adjusted to be level with the lower part of the subject's sternum. An array of red light emitting diodes (LEDs), 5 mm in diameter, was suspended over the pointing surface and a half-reflecting mirror was placed between the eyes of the subject and the table. Looking down at the mirror, the subject saw the virtual image of the targets in the plane of the pointing surface. With this device, the reaching hand could not occlude the virtual image of the LEDs, which prevented the subject from gaining an indirect feedback of his/her reaching accuracy. A light source was placed between the pointing table and the mirror. When turned on, it allowed the subject to see his/her hand. Vision of the hand was circumscribed, however, to the starting location area (a small window was opened in a black cardboard placed below the mirror, thus preventing the subject from seeing the actual location of the hand at the end of the movement; see below). The hand starting position was located on the pointing table, in the sagittal direction (*y* axis), 200 mm in front of the subject's eye plane. The starting position was defined by a green LED. When the index fingertip was at the starting point, the forearm rested on the table in a semi-flexed position. Eight targets (red LEDs) were defined along a

Table 1 *Clinical characteristics of the group of patients with Parkinson disease*

Patient	Study	Sex	Age (years)	Motor UPDRS (off-medication) (max score 108)	Hoehn and Yahr stage (off-medication) (range 0–5)	Disease duration (years)
1	1	F	49	26	3	11
2	1	F	67	52	4	14
3	1	M	52	17	2.5	8
4	1	M	52	42	2	6
5	1	F	49	45	3	17
6	1	F	76	13	2	8
7	1	M	48	29	3	6
8	2	F	38	24	2	9
9	2	F	49	54	4	?
10	2	M	58	47	3	15
11	2	F	39	35	2	12
12	2	M	48	53	4	6

M = male; F = female.

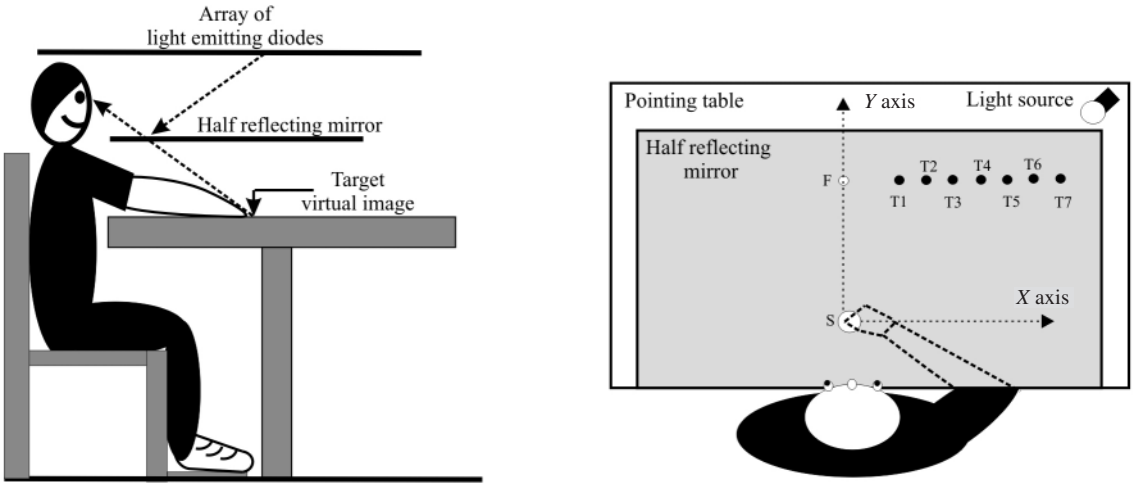

Fig. 1 Schematic representation of the experimental apparatus. S is the hand starting location and F is the visual fixation point. Black circles symbolize the location of the targets. See text for details.

fronto parallel-line (*x* axis). The sagittal distance of the 'target line' to the hand starting position was 300 mm. The first target was located in the sagittal plane (gaze fixation target; F). The other targets were positioned to the right at 160 mm (T_1), 180 mm (T_2), 200 mm (T_3), 220 mm (T_4), 240 mm (T_5), 260 mm (T_6) and 280 mm (T_7). During the experiment, the subject's head was fixed with a chin-rest and positioned along the line joining the hand starting point to the fixation target. When expressed in eye coordinates, the target eccentricities were: 17.7° (T_1); 19.8° (T_2); 21.8° (T_3); 23.8° (T_4); 25.6° (T_5); 27.5° (T_6); and 29.3° (T_7).

Movement of a small sensor located on the subject's index fingertip was recorded with a magnetic tracking system (miniBIRD; Ascencion Technology Corporation, Berlington, Vermont, USA) at a sampling frequency of 100 Hz. Eye movements were recorded binocularly using DC electro-oculography (EOG) at a sampling frequency of 1000 Hz. During the experiment, eye velocity was extracted on-line from the position signal using a two-point central difference derivative algorithm (Bahill and McDonald, 1983). For the first experiment, the change in target location in the 'jump' trials occurred when eye velocity reached a level roughly equal to half of the peak velocity. The threshold for target jump was set manually on an oscilloscope at the beginning of the experiment while the subject was required to perform a series of 25° saccades. It was adjusted during the experiment if necessary. For the second experiment, the change in target location in the 'jump' trials occurred when the hand released a small switch placed on the table at the starting location.

Experimental conditions and procedure

For the first experiment, the instruction was to 'look and point as quickly and accurately as possible to the targets presented on the table'. For the second experiment, the instruction was to 'look and point as quickly and accurately as possible to the targets presented on the table and to correct the movement, as quickly and accurately as possible, in the case of a change in the location of the target after the beginning of the trial'. For both experiments, a typical trial involved four steps.

(i) The ambient light and the green LED were turned on, allowing the subject to position his/her hand at the starting location.

(ii) The ambient light and the green LED were turned off. At the same time, the visual fixation target (F) was turned on.

(iii) After a random delay ranging between 1 and 1.5 s, the fixation point was turned off and a target was presented in the peripheral visual field instructing the subject to initiate his/her movement. The target location either remained stationary or jumped to a new location during the course of the initial motor response of the subject. Target jumps occurred only in the trials initially directed at the T_4 target (220 mm). This target, when presented, could either stay stationary, jump to the left, or jump to the right. In the first experiment, it jumped, during the saccadic gaze shift, from T_4 to T_2 (220→180 mm) or T_6 (220→260 mm). In the second experiment, it jumped, at hand movement onset, from T_4 to T_1 (220→160 mm) or T_7 (220→280). The targets that were not directly involved in these combinations (first experiment: T_1, T_3, T_5, T_7; second experiment: T_2, T_3, T_5, T_6) were mainly used as 'decoys' to increase spatial uncertainty and thus prevent the occurrence of learning and anticipatory strategies. For a given experiment, each of the decoy targets was presented five times (20 trials), while each of the relevant targets was repeated 10 times (50 trials; first experiment: T_2, T_4, T_6, T_{4-2}, T_{4-6}; second experiment: T_1, T_4, T_7, T_{4-1}, T_{4-7};). The total number of trial per session was thus equal to 70.

(iv) After completion of the pointing, the target was turned off while the ambient light and the green target were turned on again instructing the subject to bring his/her hand back to the starting point. As emphasized above, vision of the hand was only allowed in a small area around the starting location, which prevented the subject from gaining information about the accuracy of his/her former motor response.

Data analysis

The technique used for calibrating the EOG signal has been described elsewhere in detail (Pélisson *et al*., 1988). In brief, the signal was measured while the subject looked at a sequence of peripheral targets. A calibration curve was then computed by fitting a polynomial through the data. This curve was used to transform the EOG signal into a calibrated eye position signal. The eye position signal was filtered numerically at 30 Hz with a finite impulse response dual pass filter using 33 coefficients. Movement velocity was computed from the filtered position signal using a two-points central difference derivative algorithm (Bahill and McDonald, 1983). The beginning and the end of the primary saccade were automatically detected using a velocity threshold procedure (50°/s). The results of this procedure were checked off-line and corrected, if necessary. The main saccade-related parameters analysed in this experiment were the reaction time (RT_{eye}), the movement duration (MD_{eye}) and the amplitude (AMP) of the primary saccade. This parameter was expressed in absolute (AMP; gaze displacement in degrees) or relative value (AMP%; ratio of the actual to the required displacement).

For arm movements, the *x*, *y* and *z* position signals were filtered at 10 Hz with a finite impulse response dual pass filter using 33 coefficients. Movement velocity was computed from the filtered position signal using a two-points central difference derivative algorithm (Bahill and McDonald, 1983). The same method was used to compute the hand's acceleration from the velocity signal. The onset and the end of the movements were computed automatically using the following thresholds: hand velocity = 30 mm/s, hand acceleration = 500 mm/s^2. The results of this procedure were checked off-line and corrected, if necessary. The main arm-related parameters analysed in this experiment were movement reaction time (RT), movement duration (MD), movement peak velocity (PV), the movement path linearity (PL), the movement end-point location (M_{loc}), the movement final error (M_{err}), the movement end-point variability and the hand path variability. PL was defined, in the reaching plane, as the ratio of the largest deviation of arm trajectory from the line connecting the start and end points of the movement to the length of this line (Atkeson and Hollerbach, 1985). It accounted for the global movement curvature (Desmurget *et al*., 1999). The hand path linearity index is equal to 0 when the movement is perfectly straight and to 0.5 when the movement is semi-circular. Mloc was defined as the *x* (x_{loc}) and *y* (y_{loc}) coordinates of the index fingertip at the end of the movement. M_{err} was expressed in the same Cartesian reference and thus decomposed into *x* errors (x_{err}: x_{loc} minus x_{target}) and *y* errors (y_{err}: y_{loc} minus y_{target}). Movement end-point variability was represented by the 95% confidence ellipse of the end-point distribution; the lengths of the axes of this ellipse are the square roots of the eigenvalues of the variance–covariance matrix of the end-point distribution scaled to contain 95% of the theoretical end-point population (Johnson and Wichern, 1982). The end-point confidence ellipse was characterized by: (i) its surface; (ii) its shape, defined as the ratio of the lengths of the axes of the confidence

ellipses (major axis/minor axis); and (iii) its orientation, defined as the angle between the major axis of the ellipse and the movement direction (because hand paths were not straight, movement direction was defined as the orientation of the regression line computed over the last third of the trajectory). Hand path variability was represented according to a procedure described by Goodbody and Wolpert (1998). In brief, the hand position, for each movement, was re-sampled at 50 evenly spaced points along the path length. For each point of the re-sampled trajectory, a 95% confidence ellipse was computed.

Statistical analysis was performed in two steps. First, movements directed at stationary targets were compared for the Parkinson's disease patients and the control subjects. Two-way between by within subjects analysis of variance (ANOVA) design was used to determine significant differences between experimental conditions for arm and eye movement parameters. The between subject factor was the Group factor (two levels: Parkinson's disease, controls). The within subject factor was the target factor (seven levels: $T_1, T_2, T_3, T_4, T_5, T_6, T_7$). In a second step, the effect of the target jump was addressed by comparing the reference condition (T_4) to the perturbed conditions. As previously, a two-way between by within subjects ANOVA design was used. The between subject factor was the Group factor (two levels: Parkinson's disease, controls). The within subject factor was the target factor (three levels: Experiment 1: T_4, $T_{4–2}$, $T_{4–6}$; Experiment 2: T_4, $T_{4–1}$, $T_{4–7}$). The threshold for statistical significance was set at 0.05.

In addition to the these analyses, specific investigations were performed to identify the motor reaction time to the target jump (MRT) in each group. As shown in previous reports (Prablanc and Martin, 1992; Desmurget and Prablanc, 1997), variation of the characteristics of the velocity vector is the most sensitive parameter allowing determination of MRT. Therefore, this variable was used in the present study. For the sake of sensitivity, only the projection of the velocity vector in the pointing plane was considered (path corrections occurred mainly along the horizontal direction). In addition, only the perturbed conditions were studied (path corrections required opposite adjustments for the two target jump conditions, making kinematic divergences easier to detect when these conditions were contrasted with each others). In each group, the *x*–*y* coordinates of the velocity vector were determined with a temporal increment of 10 ms. For each time increment, a one-way MANOVA (multivariate analysis of variance) with repeated measure (two levels: experiment 1: $T_{4–2}$, $T_{4–6}$; experiment 2: $T_{4–1}$, $T_{4–7}$) was performed on the coordinates of the velocity vector to identify the first visible kinematic change on the trajectory (Desmurget and Prablanc, 1997). MRT was defined as the first point for which the velocity vector was different in the two perturbed conditions.

Results

Movements directed at stationary targets

Because the first and second experiments showed similar results for the movements directed at stationary targets, only the data related to the first experiment are reported below.

Eye movement characteristics

There was a trend for the Parkinson's disease patients to exhibit longer saccadic RT than the control subjects (RT_{eye}: controls = 225 ms; Parkinson's disease = 294 ms). This difference was close to the statistical threshold without reaching it [$F(1,12) = 4.4$; $P > 0.05$]. There was no effect of the target location on RT_{eye} and no significant interaction was observed for this parameter between the two experimental factors [$Fs(6,72) < 1.2$; $P > 0.30$]. In contrast to RT_{eye}, the saccadic duration was clearly independent of the group factor [MD_{eye}: controls = 79 ms; Parkinson's disease = 81 ms; $F(1,12) = 0.3$; $P > 0.55$]. However, MD_{eye} varied substantially as a function of the target location [$F(6,72) = 29.8$; $P < 0.0001$]. This parameter increased quasi linearly with the saccadic amplitude (T_1 = 70 ms; T_4 = 80 ms; T_7 = 92 ms). No significant interaction was observed for MD_{eye} between the two experimental factors [$F(6,72) = 0.2$; $P > 0.95$].

Individual saccadic responses toward stationary targets are illustrated in Fig. 2 (continuous lines). As already reported in several studies (Prablanc and Jeannerod, 1975; Harris, 1995), the oculomotor response consisted of two phases: (i) a primary

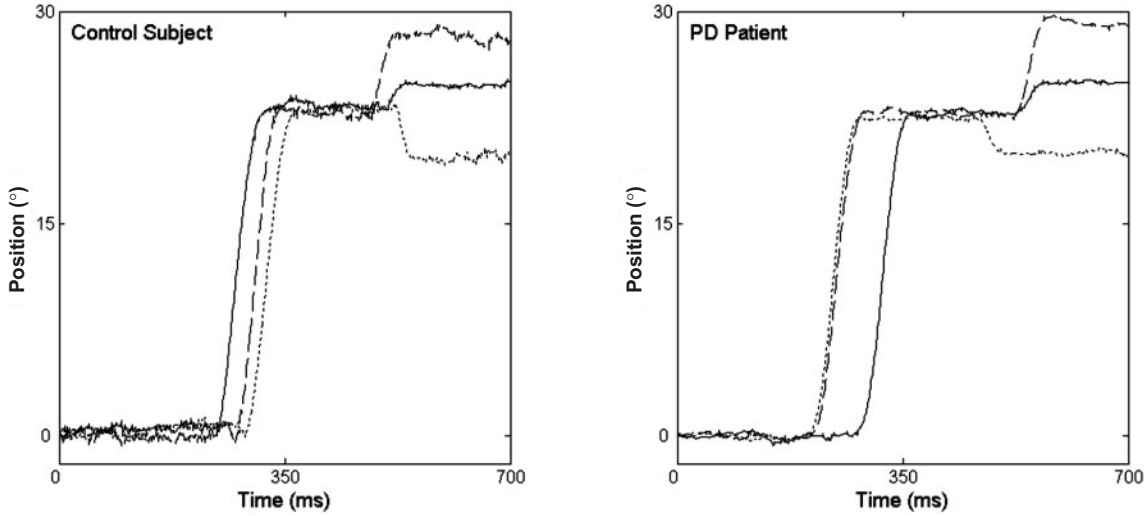

Fig. 2 Individual eye position signals recorded in the reference (T_4, continuous line) and perturbed ($T_{4–2}$, dashed line; $T_{4–6}$, doted line) conditions for a control subject (*left panel*) and a Parkinson's disease (PD) patient (*right panel*). Experiment 1: see text for details.

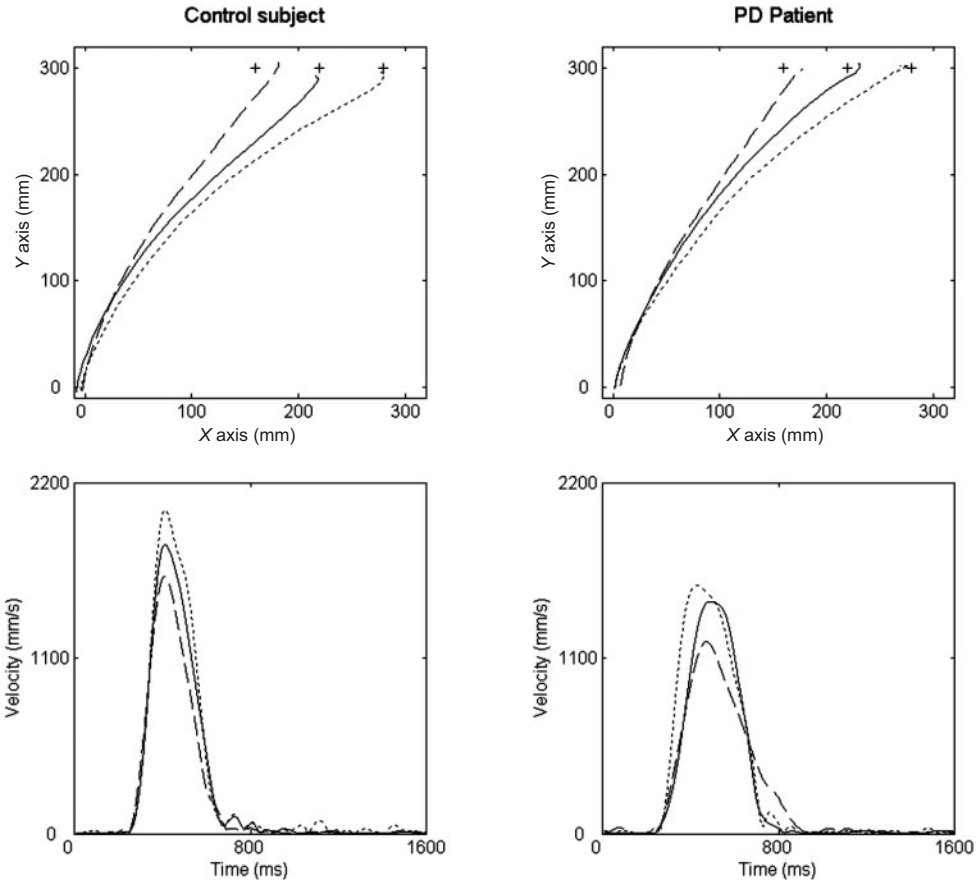

Fig. 3 Individual and path and corresponding velocity profiles exhibited by a control subject (*left panels*) and a Parkinson's disease (PD) patient (*right panels*) for movements directed to the intermediate (T_4, continuous line) and extreme (T_1, dashed line; T_7, dotted line) stationary targets. For the sake of clarity, velocity curves are aligned on movement onset. Experiment 1: see text for details.

saccade undershooting the initial target position and covering, on average, 92% of the initially required displacement; and (ii) a corrective saccade achieving accurate target acquisition. There was a tendency for the initial saccadic undershoot to be greater in the Parkinson's disease patients (AMP% = 91%) than in the control subjects (AMP% = 94%). This difference, however, did not reach the statistical threshold [$F(1,12) = 3.2$; $P > 0.10$]. In both groups, the saccadic undershoot presented a similar magnitude irrespective of the saccade amplitude, as shown by the absence of significant effect of the target factor on AMP% [$F(6,72) = 3.0$; $P > 0.10$]. This stability of AMP% produced, *de facto*, a nearly linear increase of the absolute amplitude of the primary saccade (AMP) as a function of the target location [$F(1,12) = 0.8$; $P > 0.60$; $T_1 = 16.4°$; $T_4 = 22.0°$; $T_7 = 27.2°$]. There was no significant interaction for the saccade amplitude (AMP, AMP%) between the two experimental factors [$Fs(6,72) < 1.7$; $P > 0.10$].

Hand movement characteristics

The patients exhibited longer hand RT (Parkinson's disease = 438 ms; controls = 320 ms) and hand MD (Parkinson's disease = 686 ms; controls = 527 ms) than the control subjects [$Fs(1,12) > 5.1$; $P < 0.05$]. There was no significant effect of the target location and no significant interaction between the experimental factors for these parameters [$Fs(6,72) < 1.5$; $P > 0.15$]. The increase of MD in the Parkinson's disease group was accompanied by a diminution of the peak velocity [$F(1,12) = 25.7$; $P < 0.0005$]. The absence of significant lengthening of MD as a function of the target eccentricity (i.e. the movement amplitude) was achieved by increasing the movement velocity for the targets requiring the highest movement amplitudes [$F(6,72) = 27.1$; $P < 0.0001$]. This scaling is illustrated in Fig. 3. It was similar in both groups as shown by the absence of significant interaction between the target and group factors [$F(6,72) = 1.9$; $P > 0.075$].

As illustrated in Fig. 3, both the Parkinson's disease patients and the control subjects exhibited curved hand paths. For all target locations, the movement was slightly more curved in the control group than in the Parkinson's disease population (controls = 0.058; Parkinson's disease = 0.051). This between group difference, however, did not reach the statistical threshold [$F(1,12) = 0.4$; $P > 0.55$]. A different result was observed for the target factor [$F(6,72) = 14.5$; $P < 0.0001$]; path curvature tended to increase monotonically with target eccentricity ($T_1 = 0.042$; $T_4 = 0.054$; $T_7 = 0.069$; Fig. 3). No statistical interaction was observed for the movement curvature between the experimental factors [$F(6,72) = 0.3$; $P > 0.90$], indicating

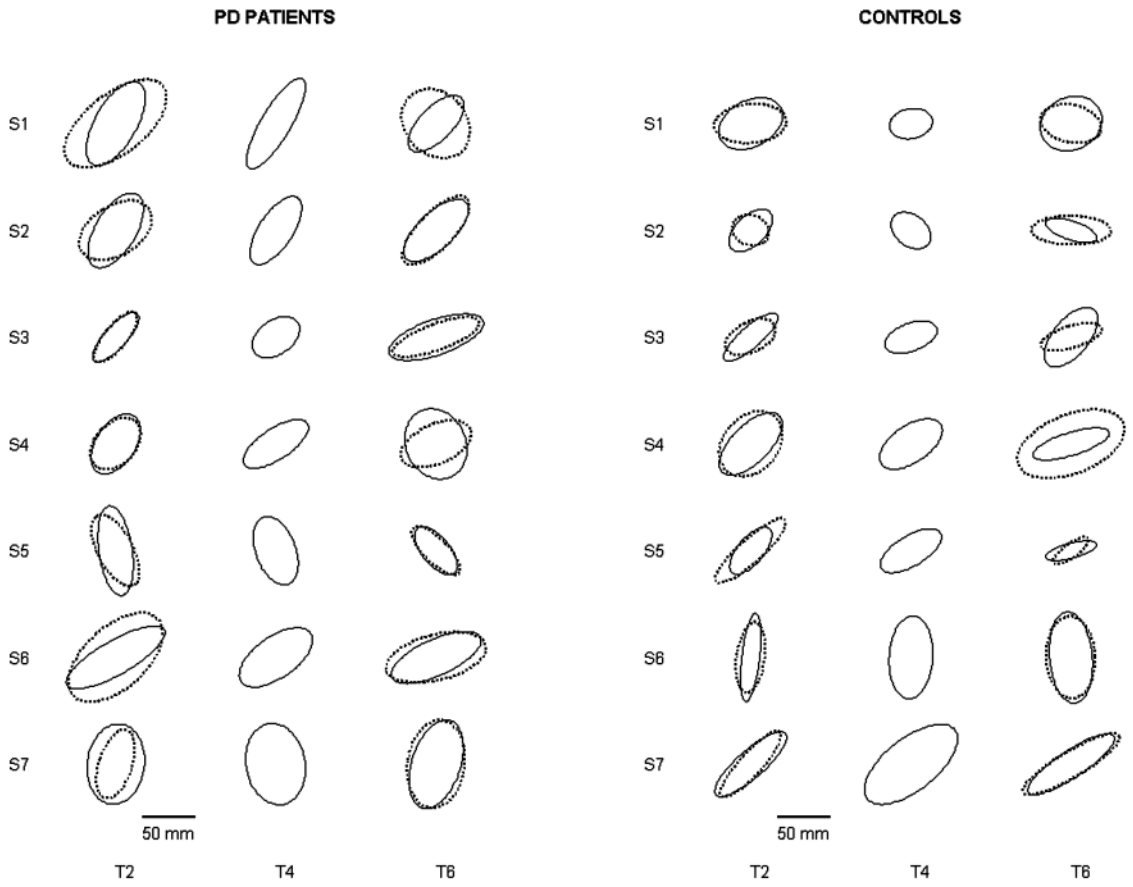

Fig. 4 95% end-point confidence ellipses exhibited by the control subjects (*left columns*) and the Parkinson's disease patients (*right columns*) for movements directed at the T_2, T_4 and T_6 stationary targets (continuous lines) and the T_{4-2} and T_{4-6} jumping targets (dotted lines).

that the effect of target eccentricity on this parameter was similar in both groups.

An interesting result with respect to the present study lies in the absence of significant difference in the mean accuracy of movement between the Parkinson's disease patients and the control subjects. As shown by statistical analyses, no effect of the group factor [$Fs(1,12) < 0.56$; $P > 0.45$] and no group by target interaction [$Fs(6,72) < 0.72$; $P > 0.60$] was observed for either x_{err} or y_{err}. Similar results have been observed in previous studies in which vision of the hand had been provided to Parkinson's disease patients prior to movement onset (Poizner *et al*., 1998; Ghilardi *et al*., 2000). We will return to this issue in the discussion.

While movement mean accuracy was not different between groups, trial-to-trial end-point variability was significantly higher in the Parkinson's disease population. On average, the surface of the end-point confidence ellipse was increased by nearly 60% in the patients with respect to the control subjects [Parkinson's disease = 2513 mm^2; controls = 1598 mm^2; $F(1,12) = 4.8, P < 0.05$]. The other parameters of the confidence ellipse did not vary significantly as a function of the group factor; in both the patients and the healthy subjects, the end-point confidence ellipse presented a typically elongated shape [Parkinson's disease = 2.9; controls = 2.6; $F(1,12) = 0.6$, $P > 0.45$], roughly oriented along the final movement direction [Parkinson's disease = 7.1°; controls = 9.8°; $F(1,12) = 0.1$, $P > 0.80$]. The surface, shape and orientation (computed with respect to the final movement direction; see Methods) of the end-point confidence ellipse were not significantly affected by the target and the interaction factors [$Fs(6,72) < 1.9$, $P > 0.10$]. These results are illustrated in Fig. 4 for all subjects and the three targets involved in the jump trials (T_2, T_4, T_6).

Not only end-point variability, but also hand path variability was larger in the Parkinson's disease patients. For instance, at the point where 40% of the total movement distance had been covered, the surface of the 95% confidence ellipse was ~75% higher in the Parkinson's disease patients than in the control subjects. This result is interesting inasmuch as it suggests that the difference in spatial variability between the patients and the control subjects was present early in the movement, i.e. that it was not related to a feedback dysfunction. Figure 5 illustrates this point by displaying hand path variability for two subjects and three 'stationary' targets (T_2, T_4, T_6; columns 2–4).

Eye–hand coordination

The previous kinematic data indicate that the arm response started around completion of the primary saccadic movement

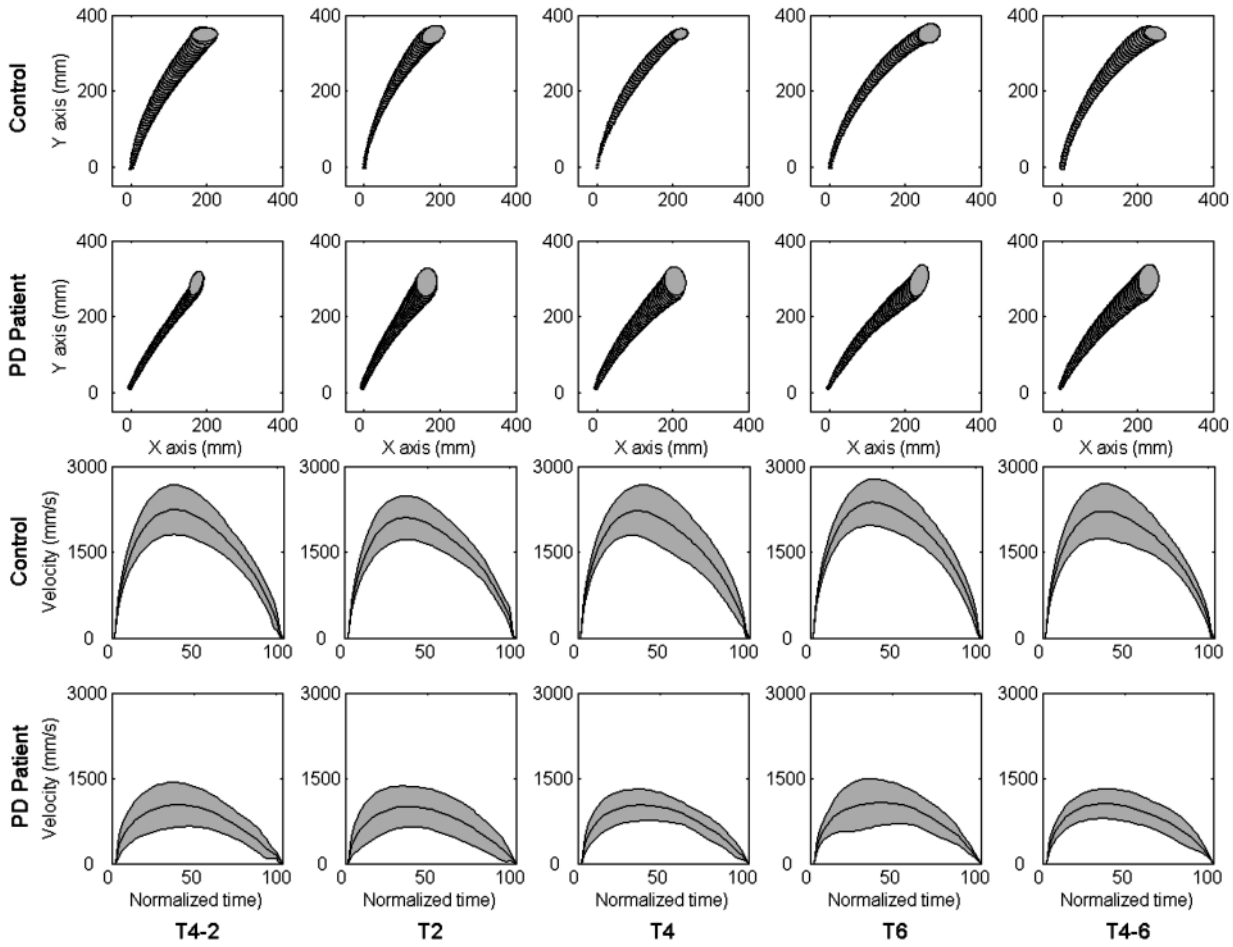

Fig. 5 95% confidence areas for the hand paths and hand velocity profiles for two representative subjects and five targets ($T_{4–2}$, T_2, T_4, T_6, $T_{4–6}$). Data were obtained by resampling hand position, for each individual movement, at 50 evenly spaced points along the path length (see methods). PD = Parkinson's disease.

in the control group [$RT_{hand} - (RT_{eye} + MD_{eye}) = 16$ ms], as reported in previous studies (Prablanc and Martin, 1992; Desmurget *et al*., 2001). A slightly different behaviour was observed in the Parkinson's disease population. In this case, hand movement was found to start later, after completion of the primary saccade [$RT_{hand} - (RT_{eye} + MD_{eye}) = 63$ ms]. However, this difference can be accounted for by previous results showing that pre-movement EMG in limb muscles is markedly lengthened in Parkinson's disease patients; the build-up of muscular activity is slowed by 50–100 ms in this population of patients with respect to healthy subjects (Godaux *et al*., 1992; Pfann *et al*., 2001). Thus, in both groups, the initial motor command sent to the arm was likely issued before visual capture of the target (i.e. on the basis of a partially inaccurate peripheral retinal input).

Movements directed at jumping targets: small subliminal target jumps (Experiment 1)

In this experiment, none of the subjects reported the existence of a change in target position during the saccadic response, even when questioned explicitly at the end of the study. In the same vein, none of the participants had the feeling of correcting the movement during its time course. Both the Parkinson's disease patients and the control subjects reported that they reached 'straight to the target'.

Eye movement characteristics

The main parameters of the primary saccadic response did not depend on any of the experimental factors. Of particular interest with respect to this result is the absence of effect of the target jump. For both the patients and the controls, the latency [RT_{eye}; $F(2,24) = 1.2$; $P > 0.30$], the duration [MD_{eye}: $F(2,24) = 0.1$; $P > 0.90$] and the amplitude [AMP, AMP%; $Fs(2,24) < 1.3$; $P > 0.25$] of the main saccade were similar in the reference (T_4) and perturbed conditions ($T_{4–2}$, $T_{4–6}$). As illustrated in Fig. 2 for a Parkinson's disease patient and a control subject, correct foveation of the target was achieved in the perturbed trials by adjusting the amplitude and the direction of the corrective saccade, which was already present in the reference condition. When the perturbation was forward ($T_{4–6}$), the target jump added with the natural saccadic undershoot resulting in a large hypometria. By

contrast, when the perturbation was backward ($T_{4–2}$), the target jump was partially cancelled by the natural saccadic undershoot creating a limited hypometria. Visual inspection of the data indicated that one corrective saccade was generally enough to achieve correct foveation in both the Parkinson's disease population and the control group. With respect to this point, however, it should be mentioned that our recording technique (EOG) did not allow reliable detection of small corrective saccades.

Hand movement characteristics

Figure 6 displays representative individual hand paths and corresponding velocity profiles for a Parkinson's disease patient and a control subject in the reference (T_4) and the perturbed conditions ($T_{4–2}$, $T_{4–6}$). As shown in Fig. 6, clear corrections occurred in both participants in response to the target jump. For $T_{4–2}$ and $T_{4–6}$, the trajectory was initially directed at the reference target (T_4) before diverging smoothly toward the new target location. These individual observations are representative of the behaviour observed at the population level for both the Parkinson's disease patients and the control subjects.

In agreement with earlier studies (Pélisson *et al*., 1986; Desmurget *et al*., 1999, 2001), hand path corrections caused a very limited and non-significant [$F(2,24) = 2.4$; $P > 0.10$] increase of the movement duration in both the Parkinson's disease (T_4 = 680 ms; $T_{4–2}$: 691 ms; T_{4-6}: 696 ms) and the control (T_4: 518 ms; $T_{4–2}$ = 531 ms; $T_{4–6}$ = 530 ms) groups. There was no group by target interaction [$F(2,24) = 0.1$; $P > 0.85$], indicating that the effect of the target jump on MD was similar in both the patient and the control populations. Interestingly, the absence of significant variation of MD as a function of the jump factor was accompanied by a clear modulation of the peak velocity [$F(2,24) = 18.1$; $P < 0.0001$]. PV tended to decrease with respect to the reference condition when the target jumped backward and to increase when it jumped forward. The effect was similar in the Parkinson's disease (T_4 = 1096 mm/s; $T_{4–2}$ = 1057 mm/s; $T_{4–6}$ = 1130 mm/s) and the control (T_4 = 1704 mm/s; $T_{4–2}$ = 1635 mm/s; $T_{4–6}$ = 1746 mm/s) groups, as shown by the absence of significant group by target interaction [$F(2,24) = 0.9$; $P > 0.40$]. This result indicates that the hand path was already affected by the target jump at the time to PV, which occurred 196 ms and 273 ms after hand movement onset in the control subjects and Parkinson's disease patients, respectively. We will return to this issue in the next section.

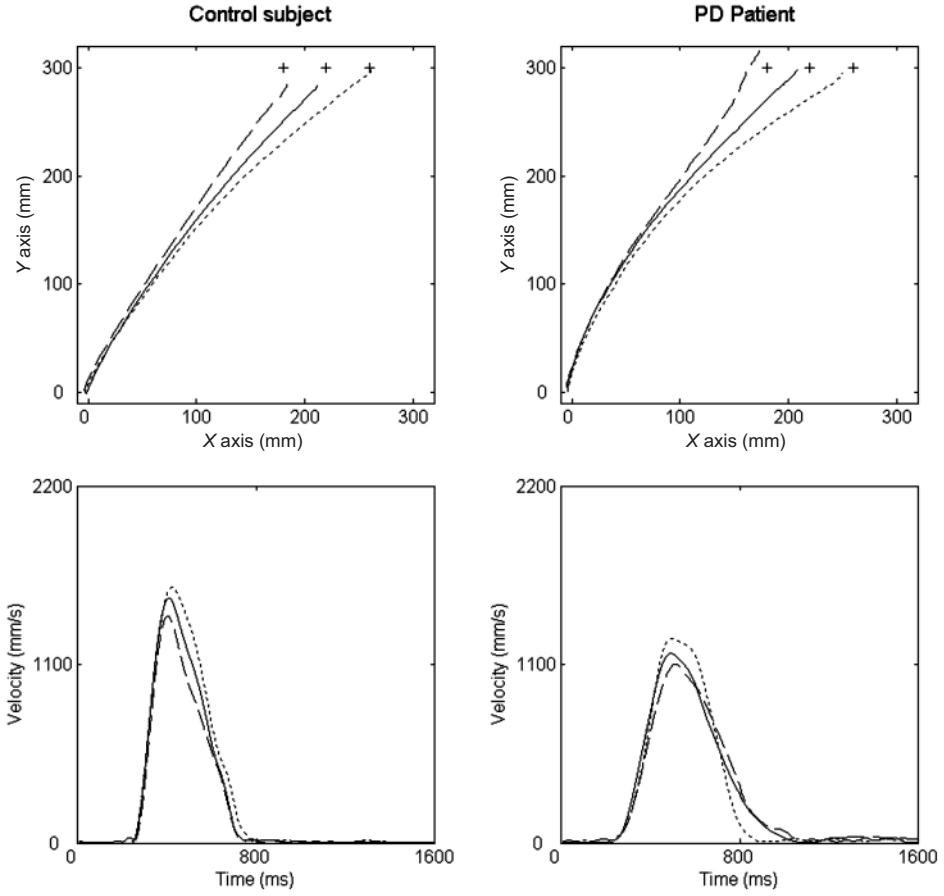

Fig. 6 Individual hand paths and corresponding velocity profiles exhibited by a control subject (*left panels*) and a Parkinson's disease (PD) patient (*right panels*) for movements directed to the reference (T_4, continuous line) and jumping targets ($T_{4–2}$, dashed line; $T_{4–6}$, dotted line). For the sake of clarity, velocity curves are aligned on movement onset. Experiment 1: see text for details.

At the spatial level, the target jump induced significant variations of the movement end-point as a function of the target factor. These variations concerned mainly the *x* component, along which the perturbation was generated [$F(2,24) = 380$; $P < 0.0001$; $T_4 = 211$ mm; $T_{4-2} = 183$ mm; $T_{4-6} = 240$ mm]. The variations observed along the *y* component did not reach the significance threshold [$F(2,24) = 1.35$; $P > 0.25$; $T_4 = 297$ mm; $T_{4-2} = 295$ mm; $T_{4-6} = 298$ mm]. No effect of the group factor [$Fs(1,12) < 0.62$; $P > 0.40$] and no group by target interaction [$Fs(2,24) < 0.32$; $P > 0.70$] was detected for either the *x* or *y* components, indicating that the between-group similarity in movement accuracy observed for stationary targets (see above) was preserved in the perturbed conditions.

Regarding movement variability, we found no evidence that feedback responses were noisier in the patient population than in the control group. No effect of the target factor and no group by target interaction was observed for the parameters characterizing the 95% end-point confidence ellipses (surface, shape, orientation) when the jumping and reference targets were compared [T_{4-2}, T_{4-6}, T_4; $Fs(2,24) < 3.0$; $P > 0.07$]. These negative results were not changed by inclusion of the final targets in the analysis [T_{4-2}, T_{4-6}, T_2, T_4, T_6; $Fs(4,48) < 1.4$; $P > 0.25$]. Specific tests were also conducted to determine whether the end-point variability could have been increased more specifically along one of the axes of the confidence ellipse or along the perturbation axis (fronto-parallel axis). These tests failed to provide a significant result. Neither the major nor the minor axis of the end-point confidence ellipses nor the end-point variability observed along the perturbation axis were found to increase as a function of the target or interaction factors [$Fs(2,24) < 1.9$; $P > 0.15$]. These results are illustrated in Fig. 4, which displays end-point confidence ellipses computed for all subjects and all targets involved in the present analysis (T_{4-2}, T_{4-6}, T_2, T_4, T_6).

The analysis of hand path variability also failed to provide support for the idea that feedback responses are noisier in the patient population. No significant effect of condition and interaction factors was observed for the surface of the spatial confidence ellipses at 20, 40, 60 or 80% of the trajectory [$Fs(2,24) < 2.1$; $P > 0.10$]. The same result was observed when hand velocity was considered. The magnitude of the confidence interval of the velocity profile did not vary as a function of the target or interaction factors at 20, 40, 60 or 80% of the trajectory [$Fs(2,24) < 1.7$; $P > 0.20$]. These results are illustrated in Fig. 5, which displays variability in hand paths and hand velocity profiles for Parkinson's disease and control subjects and for the T_{4-2}, T_{4-6}, T_2, T_4, and T_6 targets.

Hand reaction time to the target jump

For the control group, longitudinal analyses performed on the velocity vector showed that movement trajectory began to change 150 ms after hand movement onset [$F(2,5) = 7.22$; $P < 0.035$]. At this time, the velocity vector started, in particular, turning to the left in the T_{4-2} condition and to the right in the T_{4-6} condition. A slightly longer MRT was observed in the Parkinson's disease group. In this case, the first significant change was observed 180 ms after movement onset [$F(2,5) = 5.8$; $P < 0.05$]. As for the control subjects, this effect was mainly related to a rotation of the velocity vector to the left in the T_{4-2} condition and to the right in the T_{4-6} condition.

One may argue that MRT should not be computed with respect to the onset of the hand movement, but with respect to the end of the primary saccade. Indeed, it is the updating of the target location at the end of the main saccadic response that allows implementation of the required movement correction (Prablanc *et al*., 1986; Prablanc and Martin, 1992; Desmurget and Grafton, 2000). As already reported, the gap between the end of the saccadic response and the onset of the hand movement was 47 ms longer in the Parkinson's disease group than in the patient population. This indicates that the difference in MRT could be longer than the 30 ms observed when hand movement onset is considered as the time reference. When the time origin is taken at the end of the ocular saccade, MRT reaches, on average, 166 ms in the control population and 243 ms in the Parkinson's disease group. This 77 ms difference could reveal a deficit in the ability of the Parkinson's disease patients to compute the motor command required to correct the ongoing movement. Alternatively, it might also reflect the inability of these patients to implement an otherwise adequately planned correction. The logic underlying this second hypothesis is as follows: because Parkinson's disease patients have a reduced capacity to change movement acceleration (Teasdale *et al*., 1990; Godaux *et al*., 1992; Jordan *et al*., 1992; Weiss *et al*., 1997), they should also have a reduced capacity to modify quickly the direction of the hand velocity and the curvature of the hand path.

To test the latter idea and to illustrate the mathematical link existing between the changes in the direction and the extent of the acceleration vector, a simulation was conducted (Fig. 7). In this simulation, we supposed that a control subject and two Parkinson's disease patients needed the same arbitrary delay (200 ms) to plan the required correction of movement acceleration from the change in target location. The correction involved a 20° rotation of the ongoing acceleration vector. For the sake of simplicity, we supposed that the subjects planned the desired acceleration, rather than, for instance, the desired force. The maximal acceleration was arbitrarily set at 500 cm/s^2 for the control subject (Fig. 7A, bottom row, first column). For the Parkinson's disease patients, two alternatives were considered: (i) the maximal desired acceleration was equal to that of the control subject (Patient A, Fig. 7A, bottom row, second column); and (ii) the maximal desired acceleration was 30% smaller than that of the control subject (350 cm/s^2, Patient B, Fig. 7A, bottom row, third column). The second alternative was considered on the basis of behavioural results showing that Parkinson's disease patients exhibit usually smaller force and acceleration than control subjects (e.g. Flowers, 1976; Majsak *et al*., 1998; Berardelli *et al*., 2001; and the present study).

The speed in implementing a given correction was represented by a unique time constant (TC) characterizing

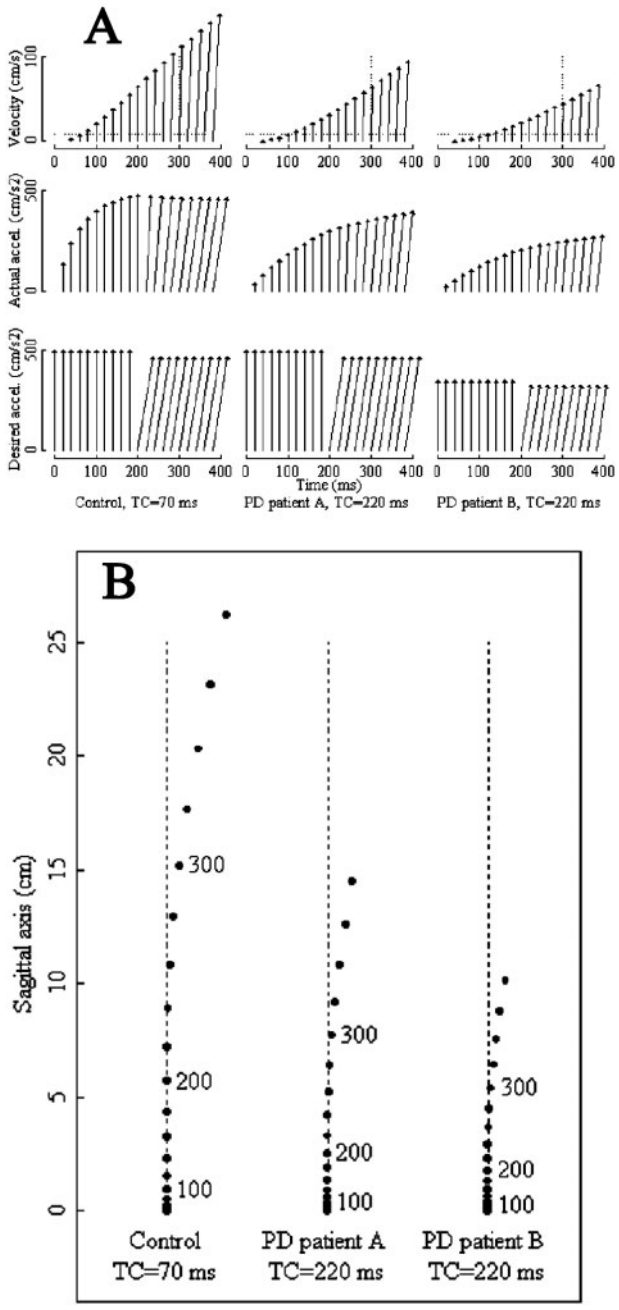

Fig. 7 Results of the simulation study carried out to illustrate the mathematical link existing between the changes in the direction and the extent of the acceleration vector. In this simulation, a control subject and two Parkinson's disease (PD) patients were supposed to need the same arbitrary delay (200 ms) to perceive a change in the target location and to plan the required correction of movement acceleration (a 20° rotation of the ongoing acceleration vector). The desired acceleration (**A**, *bottom row*) was arbitrarily set at 500 cm/s^2 for the control subject (*first column*), 500 cm/s^2 for Patient A (*second column*) and 350 cm/s^2 for Patient B (*third column*). The speed in implementing a given correction was represented by a unique TC fixed to 70 ms in the control subject and to 220 ms in the Parkinson's disease patients. Based on these time constants the actual acceleration (**A**, *middle row*) and actual velocity vectors (**A**, *top row*) were determined from the desired acceleration vector. The computed velocities were then used to assess the effects of the time constant and maximal acceleration on the hand paths (**B**). See text for details.

the quickness to change either the longitudinal or the normal component of the acceleration vector. More precisely, we supposed that if AD and AA were the desired and actual values of a Cartesian coordinate of the acceleration vector, respectively, then the derivative of this coordinate would be given by the equation dAA/dt = (AD – AA)/TC. We estimated the ratio of the time constants in the control and Parkinson's disease populations by measuring the ratio of the maximal jerk, i.e. the maximal derivative of the longitudinal component of the acceleration, in the two populations. This ratio was found to be equal to 3.14, and was consistent with the values graphically inferred from an earlier study (Godaux *et al*., 1992). In the control population, TC was fixed at 70 ms on the basis of a recent modelling study (Kashima *et al*., 2000). In the Parkinson's disease group, TC was thus estimated around 70 × 3.14 = 220 ms. Note that the results of the present simulation are much more dependent on the ratio of the time constants in the two populations than on the value chosen for the control population. The actual acceleration vector (AA) was determined from the desired acceleration vector (AD), with a 20 ms increment, by applying the equation $AA_{t+20} = AA_t + (AD - AA_t) \times 20/TC$. It can be seen in Fig. 7A (middle row) that the extent of AA increases more quickly for the control than for the patient, in agreement with the experimental observations.

The next step of the simulation was to compute velocity from the actual acceleration. As visible in Fig. 7A (upper row), the variations of the velocity vector, both in length and direction, are smaller for the Parkinson's disease patients than for the control subjects. Consequently, hand movement onset—illustrated by a horizontal dotted line—is detected earlier in the control than in the patients, and the difference is larger for Patient B (56 ms) than for Patient A (37 ms). The same tendency is observed later along the trajectory. For instance, at t = 300 ms (vertical dotted lines), i.e. 100 ms after the change in desired acceleration, velocity is 114 cm/s with a 6.3° tilt for the control, 66 cm/s with a 4.2° tilt for Patient A and 46 cm/s with a 4.2° tilt for Patient B.

As a final step, the position of the hand was derived from the computed velocities in order to assess the effects of the time constant and maximal acceleration on the hand paths. As shown in Fig. 7B, the first detectable spatial deviation with respect to the reference trajectory occurred sooner in the control subject than in the Parkinson's disease patients. For instance, the amount of spatial correction observed for the control subject at t = 300 ms is reached 40 ms and 60 ms later in Patients A and B, respectively. Note that since the patients moved more slowly than the control subject in the simulation, their hand paths started deviating from the reference direction at a point that was closer to the starting point than the point observed for the control subjects (in agreement with the present experimental observations).

In summary, the present simulation shows that any deficit in the rate of change of the muscle contractions results in both bradykinesia and slowness to execute desired directional changes. As illustrated by our data, a larger time constant in

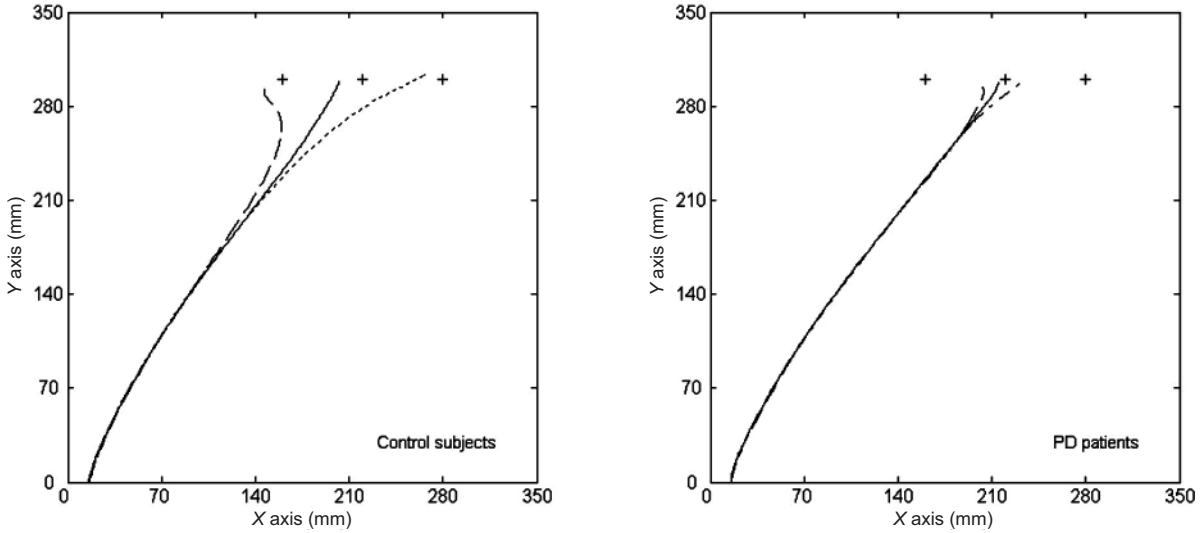

Fig. 8 Mean primary motor responses for the control (*left panel*) and the Parkinson's disease (PD) (*right panel*) populations, for movements directed to the reference (T_4, continuous line) and jumping targets (T_{4-1}, dashed line; T_{4-7}, dotted line). Experiment 2: see text for details.

changing force or acceleration causes the hand path to deviate latter from its reference trajectory. This suggest that a consistent part, if not all, of the additional delay needed by Parkinson's disease patients for reacting to the target displacement can be ascribed to movement execution deficits rather than to impairment of on-line control processes.

Movements directed at jumping targets: large consciously detected target jumps (Experiment 2)

In the second experiment, all the participants were able to identify the existence of a change in target position after hand movement onset. As reported previously (Castiello *et al*., 1991; Desmurget and Prablanc, 1997), the subjects had the subjective feeling that the target jump occurred very late, toward the end of the movement. When questioned at the end of the experiment, the control subjects reported that they had to be 'very careful' to correct the movement and avoid reaching to the first target location. The Parkinson's disease patients, by contrast, were often very frustrated with most of them claiming that they did not have enough time to correct the movement. Two patients called the task 'impossible'.

Eye movement characteristics

The characteristics of the primary saccade were not affected by the target jump, which is not surprising considering that the hand started moving after completion of the first saccade (Parkinson's disease = 67 ms; controls = 27 ms). In most cases, the corrective saccade directed toward the first target location could not be inhibited or modified. As a consequence, a third saccade was generally initiated to achieve correct foveation of the target. Interestingly, we could not find any difference in the pattern of hand movement adjustment depending on whether one or two corrective saccades were initiated. In fact, when on-line corrections were observed (see below), the first sign of modification of the ongoing hand trajectory was observed well before target foveation and even, in most instances, before the completion of the first corrective saccade (as was the case in the first experiment). This result suggests that hand and eye corrections were driven independently by the nervous system.

Hand movement characteristics

Figure 8 displays the mean hand path for the control and Parkinson's disease groups. As shown in Fig. 8, a clear modification of the ongoing trajectory was observed in the control population; the trajectories directed at the reference target (T_4) diverged progressively to reach the new target locations (T_{4-1}; T_{4-7}). These corrections were hardly visible in the Parkinson's disease population. Statistical analyses reflect this difference by showing the existence of a significant a group by target interaction for the x component of the movement end-point [the component along which the perturbation is generated; $F(2,16) = 11.0$; $P < 0.002$].

The general inability of the Parkinson's disease patients to correct their ongoing movement in response to the target jump hides some significant inter-individual differences. As shown in Fig. 9, a true absence of correction was only observed in three patients. These patients achieved target capture by generating a second movement, after completion of the primary response (Fig. 10, third column). In two other patients, clear path corrections were identified at the end of the primary movement. Interestingly, these patients exhibited movement durations (1128 and 1125 ms) that were consistently longer that the movement durations presented by the control subjects (647 ms) and the other patients who failed to exhibit any adjustment of their primary motor response (710 ms). In the Parkinson's

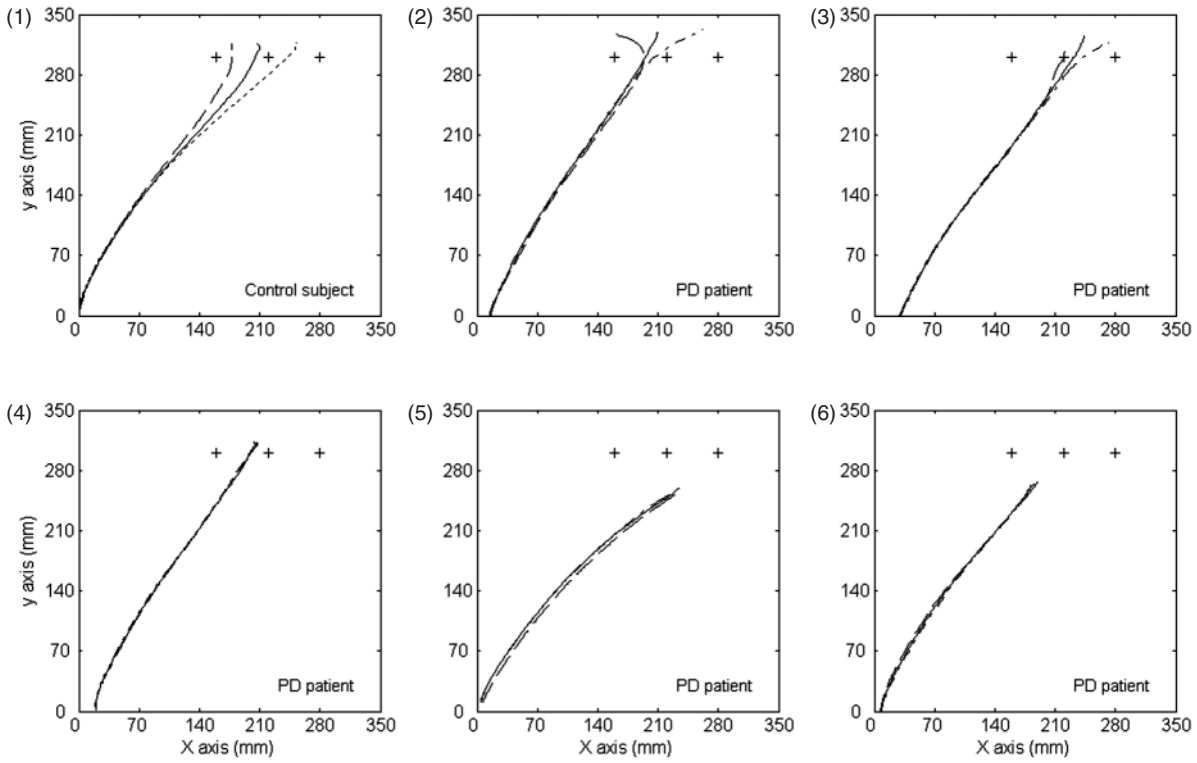

Fig. 9 Mean primary motor responses exhibited by a control subject (panel 1) and the five Parkinson's disease (PD) patients (panels 2–6) for movements directed to the reference (T_4, continuous line) and jumping targets (T_{4-1}, dashed line; T_{4-7}, dotted line). Experiment 2: see text for details.

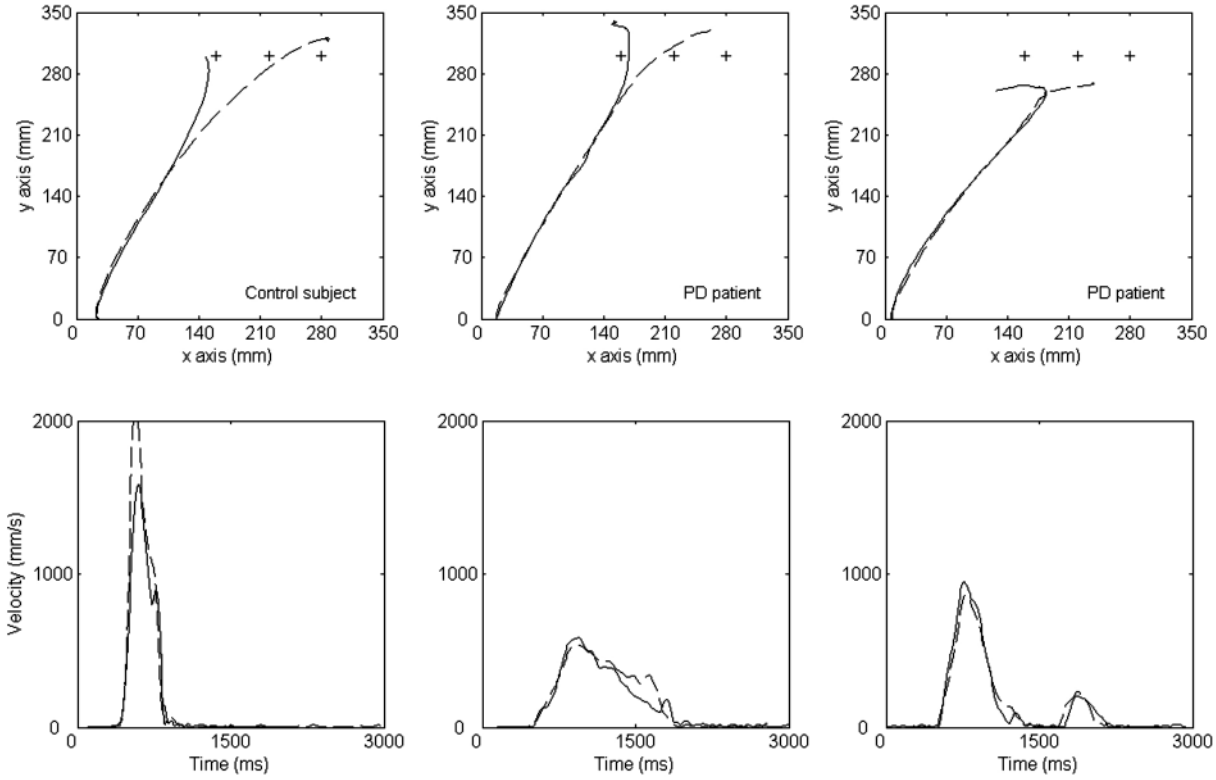

Fig. 10 Individual hand paths (*first row*) and corresponding velocity profiles (*second row*) for movements performed by a control subject (*first column*), a Parkinson's disease (PD) patient exhibiting on-line corrections (*second column*) and a Parkinson's disease patient exhibiting no corrections (*third column*). For the sake of clarity, velocity curves are aligned on movement onset. Experiment 2: see details in text.

disease patients, the path corrections caused the occurrence of clear discontinuities on the velocity profiles (Fig. 10, second column), in contrast to what was observed in the first experiment. Although less marked, these discontinuities were also present in the control population (Fig. 10, first column).

Hand reaction time to the target jump

For the control group, longitudinal analyses performed on the velocity vector showed that the perturbed trajectories started to diverge 220 ms after hand movement onset [$F(2,3) = 9.6$; $P < 0.05$]. For the Parkinson's disease population, no significant divergence time could be identified due to the absence of corrections in three of the five patients.

In order to estimate the reaction time to the perturbation in the Parkinson's disease population, a less sensitive within-subject approach was used. In the two subjects who exhibited path corrections, the perturbed trajectories were found to diverge after 730 and 910 ms, respectively (when the same within-subjects analyses were used in the control population, a mean value of 294 ms was identified). For the three subjects who failed to exhibit any modification of the ongoing trajectory, the instant of initiation of the second corrective response was determined with respect to the instant of completion of the primary movement. A mean value of 563 ms was found. This value is close to the initial movement RT, which reached 527 ms for the Parkinson's disease population in the present experiment. This suggests that these patients had to wait until completion of the ongoing movement to generate another entirely new corrective response. We did not find any relation between the severity of the disease (as measured by the UPDRS motor score) and the impairment in generating movement corrections.

Discussion

The main aim of the present study was to elucidate the contribution of the basal ganglia-thalamocortical network to the process allowing correction of the ongoing motor command. In a first experiment, we showed that Parkinson's disease patients, who present with a severe dysfunctioning of the whole basal ganglia network, are easily able to correct their ongoing trajectory when small subliminal target jumps are generated during gaze shift (a paradigm that mimics the nature of the slight automatic corrections that occur in normal movements directed at stationary targets). This result is inconsistent with previous observations gathered for Huntington's disease patients (Smith *et al*., 2000). To elucidate the origin of this inconsistency, we performed a second study under the assumption that the relevant factor explaining the difference between our data in Parkinson's disease patients and the observations already published for Huntington's disease patients did not lie in the nature of the disease, but in the characteristics of the corrections to be performed. This prediction was tested by investigating a task requiring corrections of the same type as those used previously for Huntington's disease patients, namely large consciously detected errors. Results showed that the Parkinson's disease patients had great difficulties performing this task. These results and their main implications are discussed below.

Feedback loops involving a smooth modulation of the ongoing motor command are preserved in Parkinson's disease patients

In the present study, the Parkinson's disease patients were easily able to correct their ongoing response when the target location was modified during gaze shift. The only noticeable difference observed between the patients and the controls lay in a lengthening of the time required to react to the target jump (77 ms). As shown by a simulation study, this lengthening is likely to reflect, for a substantial part (if not all), the inability of the Parkinson's disease patients to rapidly modify movement force. While Parkinson's disease patients are able to generate a desired force level quite accurately in the absence of stringent time constraints, they are not able to reach a given level of force with the same temporal characteristics as healthy subjects (Stelmach and Worringham, 1988). This deficit concerns mainly the rate of force development (Teasdale *et al*., 1990; Godaux *et al*., 1992; Jordan *et al*., 1992) and force release (Wing, 1988; Kunesch *et al*., 1995). It results *de facto* in a slowed execution each time a force change has to be implemented. From these observations, one may conclude that the non-visual feedback loops allowing smooth modulation of the ongoing motor command are well preserved, if not normal, in the patient population. Additional indirect evidence supporting this view can be found in the observation that adjustments observed in the perturbed trials did not cause the movement duration to increase, as would be expected if the ability to detect or implement the required correction was severely impaired in the Parkinson's disease patients.

The idea that the non-visual feedback loops allowing a smooth modulation of the ongoing response are preserved in Parkinson's disease patients is also supported by the kinematic characteristics of the movements directed at stationary targets. In the present study, we provided evidence that the motor command sent to the arm was issued prior to target foveation in both the Parkinson's disease patients and the control subjects. This indicates that the initial motor response engaging the upper limb was computed, in both groups, on the basis of an inaccurate peripheral visual signal (Prablanc *et al*., 1979; Bock, 1993). In healthy subjects, it has been repeatedly demonstrated that this initial inaccuracy was corrected on-line when the system had the opportunity to update the target location at the end of the saccadic response and as was the case in the present study (Prablanc *et al*., 1986; Desmurget and Grafton, 2000). In light of this result, the fact that end-point accuracy was not significantly different, for the unperturbed trials, in the control subjects and the Parkinson's disease patients can be considered as an additional (even if indirect) evidence that on-line feedback loops were neither disrupted nor dramatically biased in the Parkinson's disease population. With respect

to this conclusion, it is also worth noting that the absence of increase of the movement end-point variability in the 'jump trials' fits well with the idea, emphasized in the Introduction, that similar feedback loops are engaged in the control of movements directed at stationary and subliminally displaced targets.

One may question the results above based on the report of dramatic end-point errors in Parkinson's disease patients for reaching movements performed in the dark (Flowers, 1976). We suggest that the possibility to see the hand at rest in the present experiment explains the good accuracy displayed by the patients. Indeed, end-point errors during reaching movements reflect, for a large part, systematic biases in the estimation of the initial hand location (Rossetti *et al*., 1995; Vindras *et al*., 1998). As shown in several studies, when vision of the hand at rest is allowed, the localization errors and hence the end-point errors decrease dramatically with respect to a condition where vision of the hand is prevented (Ghez *et al*., 1995; Vindras *et al*., 1998; for a review, see Desmurget *et al*., 1998). Without vision of the stationary hand, estimation of the initial state of the motor apparatus relies on static proprioception alone. Since this sense is impaired in Parkinson's disease patients (Schneider *et al*., 1987; Jobst *et al*., 1997; Zia *et al*., 2000), one might predict that the effect on movement accuracy of not seeing the hand at rest will be more dramatic in a group of Parkinson's disease patients than in a group of control subjects. Two studies by Flowers (1976) and Ghilardi *et al*. (2000) support this view. In both studies, the subjects were required to move a cursor in the horizontal plane without seeing their limb. Starting and target positions were presented on a vertical screen. In the Flowers study, the starting location was hidden before target presentation, thereby favouring 'localization errors'. A dramatic alteration of end-point accuracy was then observed in Parkinson's disease patients. In contrast, the starting location was always visible in the study by Ghilardi and colleagues. This allowed patients to minimize 'localization errors'. No accuracy degradation was reported in this case, in agreement with our own observations. Note that a preserved movement accuracy was also observed by Poizner *et al*. (1998) in a study allowing vision of the hand at rest and involving unrestrained reaching movements directed at memorized targets.

The absence of significant accuracy degradation in the patient population is also puzzling if one considers: (i) that parkinsonism causes significant impairments of the dynamic proprioceptive sense (Klockgether *et al*., 1995; Demirci *et al*., 1997); and (ii) that on-line feedback loops make use of dynamic proprioception (Cordo, 1990; Wolpert *et al*., 1995; Bhushan and Shadmehr, 1999). Obviously, if proprioception is both biased and used to guide the hand to the target, movement end-point should be affected. In line with this idea, it was in particular suggested that the hypometria often exhibited by Parkinson's disease patients could be explained by a proprioceptive deficit causing the distance covered by the arm to be overestimated (Moore, 1987; Klockgether *et al*., 1995; Demirci *et al*., 1997). The results of the present experiment seem inconsistent with this claim (see also Poizner *et al*., 1998; Ghilardi *et al*., 2000). A potential explanation to this discrepancy might be that the proprioceptive deterioration was too marginal in our patients to significantly bias movement accuracy. An alternative interpretation could be that on-line feedback loops dealing with small errors in the estimation of the target location do not rely on the proprioceptive input, but mainly on the efferent signal. Evidence supporting this interpretation have been presented elsewhere (Desmurget and Grafton, 2000; Desmurget *et al*., 2003).

Recent studies showing that automatic reach adjustments are cortically organized in humans also support the view that the basal ganglia network does not provide an essential contribution to the non-visual feedback loops that mediate smooth corrective modulations of the ongoing motor commands (for a review, see Desmurget and Grafton, 2000, 2003). A recent PET imaging study showed that hand path corrections involved a restricted network engaging the posterior parietal cortex, the primary motor cortex and the anterior parasagittal cerebellar cortex (Desmurget *et al*., 2001). No contribution of the basal ganglia network could be identified, even when the statistical analyses were conducted at an unusually permissive threshold ($P = 0.01$, uncorrected for multiple comparisons). In agreement with this result and with the idea that the ability to modulate the ongoing motor command is a cortically mediated function, recent studies have shown that smooth on-line movement corrections were disrupted when the contribution of posterior parietal cortex to this function was disrupted either due to a lesion (Pisella *et al*., 2000; Grea *et al*., 2002) or the application of a transcranial magnetic pulse at hand movement onset (Desmurget *et al*., 1999).

Iterative on-line motor control is severely impaired in Parkinson's disease patients

In the present study, the control subjects were easily able to correct for large consciously detected target jumps generated at hand movement onset. The corrections, which started to influence the ongoing trajectory after only 220 ms, produced perceptible discontinuities in the velocity profiles. These discontinuities are generally thought to reflect the generation of discrete sub-movements that overlaps with the ongoing response (Meyer *et al*., 1988; Novak *et al*., 2002). As shown in several modelling studies, this 'overlapping' can be characterized as a composite of several sub-movements, each of which represents a scaled version of a prototypic 'ballistic' entity (Flash and Henis, 1991; Milner, 1992). Interestingly, the Parkinson's disease patients were dramatically impaired when generating this type of iterative corrections. Three patients had to wait until completion of the initial motor response before initiating a corrective action. The latency of this correction was roughly equal to the reaction time observed for the movements directed at stationary targets. This suggests that the corrective sub-movements could not be implemented in parallel with the ongoing action. In two other patients, some overlap was observed. However, these patients presented with unusually long movement durations

(>1.1 s) and with abnormally slow corrective reaction times (730 and 910 ms, respectively). One may not exclude the hypothesis that the increased movement duration reflected, in these patients, a deliberate strategy to deal with the potential occurrence of target jumps.

Our results are consistent with observations in Huntington's disease (Smith *et al*., 2000) and with indirect evidence suggesting that subcortical structures may be involved in the corrections of large consciously detected errors (Day and Brown, 2001). With respect to this conclusion, however, it is important to recognize that impairments associated with basal ganglia pathology, such as those described here, may arise either from loss of a normal basal ganglia function *per se* or, equally likely, from disruption of downstream brain regions secondary to aberrant inhibitory output from a pathologic basal ganglia (Wichmann and DeLong, 1998; Berardelli *et al*., 2001). It is also essential to bear in mind that, in advanced Parkinson's disease, pathology is not restricted to the basal ganglia–thalamocortical circuits (Braak *et al*., 2000). These experiments do not provide information on the exact contribution of these different circuits.

Two main, non-exclusive hypotheses can be proposed with regard to the root cause for the dramatic impairment of iterative corrections in Parkinson's disease patients. First, Parkinson's disease patients need significantly more time than control subjects to initiate reaching movements. In our study, for instance, the movement reaction time was 37% longer in the patient population than in the control group. This akinesia is likely to affect the ability to implement iterative path corrections by lengthening the time required to initiate the corrective sub-movement. Secondly, Parkinson's disease patients experience significant troubles when required to string together successive motor acts (Cools *et al*., 1984; Benecke *et al*., 1987; Agostino *et al*., 1992). Of particular interest with respect to this point is the apparent difficulty of Parkinson's disease patients to switch from one coordinated movement to another (Giladi *et al*., 1992, 1997; Weiss *et al*., 1997; Almeida *et al*., 2003). This difficulty worsens in situations where the movement sequence is not known in advance (Curra *et al*., 1997), as is the case when a corrective sub-movement has to be generated and added to the current movement in response to a motor error. Within this context, the difficulty of Parkinson's disease patients to generate iterative motor corrections may be seen as the expression of their more general inability to execute sequential and simultaneous actions.

Distinct corrective processes coexist in the motor system

The idea that distinct control processes coexist in the brain has been questioned in several modelling studies, suggesting that a single iterative model may account for smooth correction patterns provided that the corrective movement is small with respect to the initial motor response (Flash and Henis, 1991; Hoff and Arbib, 1993; and Feldman and Levin, 1995). Although mathematically efficient, these models are hard to reconcile with recent behavioural results arguing for the existence of an automatic feedback mechanism that would not act by generating an independent corrective sub-movement, but by modulating the ongoing motor command (Desmurget and Grafton, 2003; Prablanc *et al*., 2003). Within this context, a correction of the movement magnitude would, for instance, not be achieved by planning a new corrective response but simply by prolonging the duration of the initial agonist burst. In agreement with this view, subtle on-line modulations of the EMG activity have been described during goal-directed movements (Angel 1975, 1977; Hallett and Marsden, 1979; Flanders *et al*., 1996). In addition, our data indicate that a dramatic impairment in the ability to generate iterative corrections does not prevent Parkinson's disease patients from smoothly updating the ongoing trajectory. This deficit mirrors nicely the deficit exhibited by a patient presenting with a bilateral posterior parietal lesion (Pisella *et al*., 2000), which showed that automatic feedback control was absent in this patient, despite her preserved ability to plan reaching movements to visual targets. Compatible observations were recently found in a PET study (Desmurget *et al*., 2001), which showed that the smooth path adjustments studied in experiment 1 engage a set of areas that is marginal with respect to the large network required to plan a motor response.

Based on the evidence presented above, it may be tempting to speculate that there is a functional limit to motor flexibility. When this limit is reached, the required correction can no longer be achieved by smoothly modulating the ongoing motor command and a discrete corrective sub-movement is generated instead (Desmurget and Prablanc, 1997). This may happen when the error to be corrected is either too large or too late, as was the case in our second experiment with respect to the first one. Indeed, in the second experiment, the target jump was larger (60 versus 40 mm) and delayed by $\sim$70 ms and 15 ms in the patients and controls, respectively; these delays correspond to the mean delays between the end of the saccadic shift and the onset of the hand movement.

Beyond the magnitude and the instant of occurrence of the target jump, the ability to consciously perceive the ongoing error might also be a critical factor explaining the transition from a smooth automatic control to an iterative strategy. With respect to this idea, one may speculate that awareness of an error overrules the automatic control regulations to impose an 'abort-and-replan' scheme. A more general formulation of this (speculative) hypothesis might be that different control policies coexist in the brain. Computationally, a control policy defines the type of feedback control law that has to be implemented in response to a given situation (Kirk, 1970). For instance, based on the assumption presented in the Introduction that movements directed at stationary and subliminally displaced targets are functionally identical (experiment 1), one may hypothesize that the same control policy is used irrespective of the type of trials (jump versus stationary). This control policy might require, for instance, to move the hand as smoothly as possible to the target (Hoff and Arbib, 1993). In experiment 2, the existence of a large consciously perceived

target jump might make the initial control policy incompatible with the level of error that is tolerable. As a consequence, the target jump might cause the ongoing policy to be abandoned for a new policy. If such a change in the ongoing control policy is allowed on the basis of a measure of estimated reward potential (i.e. 'will the movement be successful'), then segmentation in action can be observed. With respect to this point, it is tempting to speculate that the delay underlying the change in control policy might be increased in Parkinson's disease patients (due, for instance, to a difficulty in estimating the potential reward of the ongoing movement), thus increasing the difficulty of these patients to perform the large conscious corrections investigated in the second experiment.

Forward modelling and the basal ganglia network

On-line feedback control is generally thought to rely on a forward model (see Introduction). Provided this (well substantiated) hypothesis is true, one may suggest on the basis of experiment 1 that the process of forward modelling is preserved in Parkinson's disease patients. This conclusion is coherent with recent reports showing fairly sound tracking abilities in Parkinson's disease patients (Bloxham *et al*., 1984; Day *et al*., 1984; Liu *et al*., 1999). It is also in accord with the preserved ability of Parkinson's disease patients to use visual feedback loops to guide ongoing movements (Flowers, 1976; Flash *et al*., 1992; Ghilardi *et al*., 2000).

Based on the previous remarks, it is tempting to conclude that the deficit exhibited by the Parkinson's disease patients in experiment 2 is not related to a deficit in forward modelling and hence that the basal ganglia network is not involved in this type of predictive behaviour. Although plausible, this conclusion remains questionable for two main reasons. First, the present study did not involve any specific component that tested directly the issue of forward modelling. Secondly, a deficit in the ability to generate a forward model is compatible with the type of difficulties exhibited by the Parkinson's disease patients in experiment 2. Indeed, due to the existence of non-linearities in the motor plant, the summation of motor commands is not linear, meaning that an identical command pulse given at different times during a movement produces different results. In order to add successive movements, it is therefore necessary to estimate (in real time) the position and speed of the limb and hence to rely on a forward model of the arm's dynamics (Novak *et al*., 2002). When the process of forward modelling is impaired, estimation of the hand location has to be based on proprioception. This sensory-based estimation is thought to be reliable only when velocity is null (i.e. after movement completion) or low (i.e. toward the end of the movement) (Hollerbach, 1982; Gerdes and Happee, 1994). A deficit in forward modelling could thus explain the pattern of corrections exhibited by the Parkinson's disease patients in experiment 2.

Based on the discussion above, one may not exclude the hypothesis that different neural networks are recruited to estimate the state of the motor apparatus in experiments 1 and 2. This idea is compatible with the fact, already mentioned, that a larger set of areas is engaged when a new movement has to be planned with respect to a situation in which the ongoing command is only slightly modulated (Desmurget *et al*., 2001; Desmurget and Grafton, 2003). Further studies are required to investigate this possibility.

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