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RESEARCH ARTICLE

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Basal ganglia network mediates the control of movement amplitude

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Abstract In the present study we address the hypothesis that the basal ganglia are specifically involved in the planning of movement amplitude (or related covariates). This prediction has often been put forward based on the observation that Parkinson's disease (PD) patients exhibit hypokinesia. A close examination of the literature shows, however, that this commonly reported clinical symptom is not consistently echoed by experimental observations. When required to point to visual targets in the absence of vision of the moving limb, PD subjects exhibit various patterns of inaccuracy, including hypometria, hypermetria, systematic direction bias, or direction-dependent errors. They have even been shown to be as accurate as healthy, age-matched subjects. The main aim of the current study is to address the origin of these inconsistencies. To this end, we required nine patients presenting with advanced PD and 15 age-matched control subjects to perform planar reaching movements to visual targets. Eight targets were presented in equally spaced directions around a circle centered on the hand's starting location. Based on a previously validated parsing procedure, end-point errors were segmented into localization and planning errors. Localization errors refer to the existence of systematic biases in the estimation of the initial hand location. These biases can potentially transform a simple pattern of pure amplitude errors into a complex pattern involving both amplitude and direction errors. Results indicated that localization errors were different in the PD patients and the control subjects. This is not surprising knowing both that proprioception is altered in PD patients and that the ability to locate the hand at rest relies mainly on the proprioceptive sense, even when vision is available. Unlike normal subjects, localization errors in PD were idiosyncratic, lacking a consistent pattern across subjects. When the confounding effect of initial hand localization errors was canceled, we found that end-point errors were only due to the implementation of an underscaled movement gain (15%), without direction bias. Interestingly, the level of undershoot was found to increase with the severity of the disease (inferred from the Unified Parkinson's Disease Rating Scale, UPDRS, motor score). We also observed that movement variability was amplified (32%), but only along the main movement axis (extent variability). Direction variability was not significantly different in the patient population and the control group. When considered together, these results support the idea that the basal ganglia are specifically involved in the control of movement amplitude (or of some covariates). We propose that this structure participates in extent planning by modulating cortical activity and/or the tuning of the spinal interneuronal circuits.

Keywords Parkinson's disease · Basal ganglia · Reaching · Movement amplitude · Movement accuracy

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Introduction

It is generally admitted that hypokinesia is a cardinal sign of parkinsonism. In classic textbooks or dedicated reviews, this terms refers to the tendency of Parkinson's disease (PD) patients to exhibit reduced movement amplitude in various tasks such as handwriting (micro-

graphia) or hand pointing (hypometria; Berardelli et al. 2001; Denny-Brown 1968; Petit et al. 1995). Curiously, this standard clinical symptom is not always echoed by experimental observations. In particular, while some studies have reported systematic hypometria when vision of the moving limb is occluded (Flowers 1976; Klockgether and Dichgans 1994), others have shown that the tendency to undershoot the target was either absent (Ghilardi et al. 2000) or dependent on the movement direction (Flash et al. 1992). In the same vein, although some experiments have only identified amplitude errors during hand reaching (Klockgether and Dichgans 1994), others have described both amplitude and direction errors (Flash et al. 1992). The main aim of the present study is to reevaluate these issues and determine the nature of the errors exhibited by patients presenting with advanced PD. Our hypothesis is that the basal ganglia (BG) are specifically involved in the planning of movement amplitude (or related covariates). If this is the case, PD patients should exhibit a selective inability to adjust movement gain, i.e., to match the amplitude of the movement with the eccentricity of the target.

When trying to determine whether PD patients exhibit a specific impairment in movement amplitude, the first idea that comes to mind is to decompose the movement end-point error into an amplitude error and a direction error. In this case, the amplitude error is defined as the difference between the actual movement amplitude and the required movement amplitude; the direction error is defined in the same way as the angular difference between the actual movement direction and the required movement direction. Unfortunately, this "obvious" procedure is misleading.

The problem is that amplitude and direction errors will only identify erroneous planning of movement amplitude and/or movement direction if there is no bias in the estimation of the initial hand location. This assumption is generally not valid. Indeed, recent studies have demonstrated that reaching errors reflect not only planning deficits. A large source of error can be due to systematic biases in the estimation of the initial hand location (Desmurget et al. 1999; Rossetti et al. 1995; Sainburg et al. 2003; Vindras et al. 1998; for a review, Desmurget et al. 1998). Localization errors can potentially transform a simple pattern of pure amplitude error into a complex pattern involving both amplitude and direction errors (Vindras et al. 1998). The problem is critical in the context of the present study considering both that proprioception is altered in PD patients (Demirci et al. 1997; Jobst et al. 1997; Klockgether et al. 1995; Schneider et al. 1987; Zia et al. 2000) and that the ability to locate the hand at rest relies mainly on the proprioceptive sense, even when vision is available (Desmurget et al. 1999; Rossetti et al. 1995; van Beers et al. 1996).

It is theoretically plausible that the large errors exhibited by PD patients in the dark are not reflective of an executive deficit, but mainly of an inability to estimate the state of the motor system prior to movement onset. Similarly, it is also possible that some contradictory results reported in the literature are related to unidentified variations in the subjects' ability to locate their hand at rest. Two studies, by Flowers (1976) and Ghilardi et al. (2000), illustrate this point. 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 favoring "localization errors." A dramatic alteration of end-point accuracy was then observed in PD patients. In the Ghilardi et al. study, by contrast, the starting location was always visible, which allowed patients to minimize "localization errors," and no accuracy degradation was reported.

In summary, there is still a lively debate regarding the nature and origin of the reaching errors exhibited by PD patients. The present experiment addresses this issue with the purpose of testing the hypothesis that the BG are specifically involved in the planning of movement amplitude (and covariates). In agreement with this prediction, we show that PD patients exhibit pure amplitude errors compared with control subjects after pointing errors arising from an erroneous estimation of the initial hand location are taken into account.

Methods

Subjects

Nine patients (four women and five men; mean age ± SD: 61±11 years) and 15 control subjects (eight women and seven men; mean age ± SD: 55±9 years) took part in the study, after their informed consent was obtained. The age difference observed between the two groups was not statistically significant (t=1.4; P>0.15). The subjects were all right-handed and the experimental procedure was approved by the Human Investigations Committee of Emory University. Neither the parkinsonian nor the control subjects presented evidence of dementia, cognitive impairments, or other neurological disorders. The patients enrolled in this study were at a severe stage of the disease. They all had been under L-dopa treatment for more than 5 years and they were under consideration for surgical treatment. The patients did not exhibit major signs of tremor. At the time of evaluation they had been off medication for more than 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 UPDRS were determined before the experiment by one of the movement-disorders specialists at our institution. UPDRS scores ranged from 14.5 to 46 (mean 30, SD 11). Hoehn and Yahr scores ranged from 1 to 4.5 (mean 3, SD 1). Table 1 summarizes the main clinical features of the patients.

Apparatus

A schematic representation of the experimental apparatus used in the present study is presented in Fig. 1. This apparatus was similar to the one employed in previous experiments (Desmurget et al. 1997, 1999, 2000). In brief, it consisted of a horizontal digitizing table to record the planar movements of a computer-like mouse held by the subjects (200 Hz sampling rate, ±0.05 mm resolution). The height of the table was adjusted to be level with the lower part of the subject's sternum. The subject's head was free to move. An array of light-emitting diodes (LEDs; diameter 5 mm) and a half-reflecting mirror were suspended over the pointing surface.

Table 1 Clinical characteristics of the group of patients with Parkinson disease (*H&Y* Hoehn and Yahr, *med* medication, *UPDRS* Unified Parkinson's Disease Rating Scale)

Patients	Sex	Age (years)	Motor UPDRS (off med)	H&Y stage (off med)
PD 1	M	69	35.5	4.0
PD 2	M	50	14.5	3.0
PD 3	M	52	24.0	1.0
PD 4	F	47	28.5	3.0
PD 5	M	48	34.5	3.5
PD 6	M	71	34.0	3.0
PD 7	F	69	39.0	4.5
PD 8	F	72	15.5	3.0
PD 9	F	69	46.0	3.0

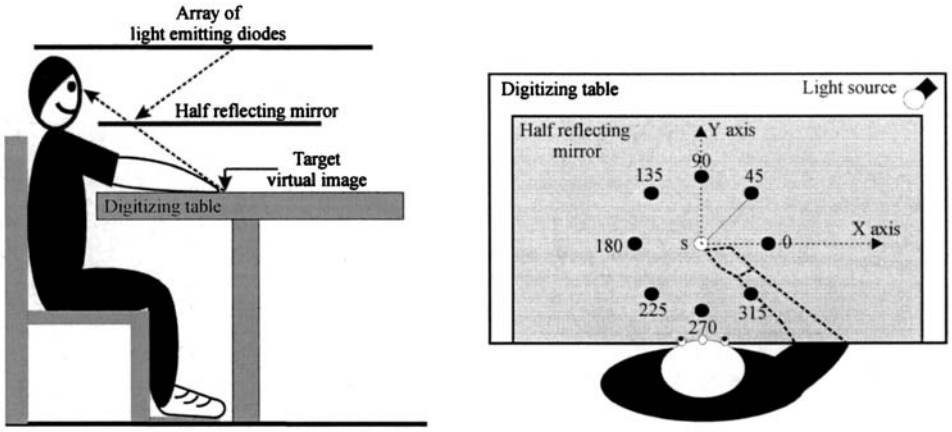

Fig. 1 Schematic representation of the experimental apparatus

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 their reaching accuracy. A light source was placed between the pointing table and the mirror. When turned on, it allowed the subject to see their hand. The hand starting position (S) was located on the pointing table, in the sagittal plane, 30 cm in front of the subject's sternum. Eight targets (red LEDs) were defined around a circle centered on S (Radius, 15 cm). These targets were located at 0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315° with respect to the frontoparallel axis (counterclockwise direction). An additional green LED was positioned to appear on the table, at the hand starting location (S).

Experimental conditions and procedure:

During the experiment, the subjects were instructed to "point as quickly and accurately as possible with a single uncorrected movement." No special emphasis was put on velocity or on reaction time. At the beginning of the study, subjects were trained until they felt comfortable with both the task and the apparatus. The training session never took more than 8 trials.

A typical trial involved five steps: (1) the ambient light and green LED were turned on, prompting the subject to bring their hand to the starting point; (2) the ambient light was turned off so that the subject's arm was no longer visible. The subject was instructed to keep looking at the green LED, which indicated the initial hand location; (3) the green fixation point was turned off and the target was presented after a random fixation delay (500–1500 ms), thereby prompting the subject to move their hand to the target; (4) the experimenter moved the subject's hand about 30 cm away from its current location after completion of the pointing movement, to prevent the subject from estimating their pointing accuracy based on visual and/or motor cues; (5) the ambient light was turned on again triggering the next trial. The experiment was segmented into two sessions to allow the subject a rest period. The two identical sessions involved 40 pointing movements (5 trials for each target in random order per session). Since no effect of session was found during data analysis, this factor was disregarded in the present report. The effect of time was also disregarded inasmuch as no sign of modification of the motor performance of the subject as a function of time (trial number) was observed.

Recording technique and data analysis

An orthogonal frame of reference was defined for data analysis (Fig. 1). This frame was centered on the hand starting point S. The *y*-axis was sagittal and oriented forward; the *x*-axis was frontoparallel and oriented rightward. The *x*, *y* position signals delivered by the digitizing table were filtered at 10 Hz with a zero phase finite impulse-response filter (FIR). Movement velocity was computed from the filtered position signal, using a least-squares, second-order polynomial method. The same method was used to compute hand acceleration from the velocity signal. The onset and the end of the hand movement were determined automatically using the following threshold: hand velocity, 8 cm/s, hand acceleration, 150 cm/s^2 (the peak velocity was first determined and the curve was scanned backward and forward to determine the movement onset and the movement end). The results of this procedure were checked off-line and if necessary corrected. Because the PD patients tended to move more slowly than the control subjects, we tested whether using a single threshold for both population could bias the results. To this end we tested how lowering the threshold in the PD group might affect the data (hand velocity, 6 cm/s; hand acceleration, 120 cm/s^2). The outcome of this manipulation was marginal and without effect regarding the results of this study. As a consequence the same thresholds were used in both groups (hand velocity, 8 cm/s; hand acceleration, 150 cm/s^2)

In the present study, two-way ANOVA with repeated measures was used to identify significant differences in the movement parameters between the Parkinson patients and Control subjects. The experimental factors were Group (between factor; 2 levels: Parkinson versus Control), and Target location (repeated-measures

factor: 8 repeated levels). Because the sphericity requirements were not likely to be met by our data with repeated measures, the Box adjustment procedure for degrees of freedom was carried out (Hays 1988). The Geisser-Greenhouse estimates of the Є parameter were used. The same procedure was applied to all similar ANOVA performed in this study. Threshold for statistical significance was set at 0.05. The Tukey honest significance difference test was used for post hoc comparisons of the means.

The main movement parameters considered in this experiment are described below.

Main movement characteristics

To determine whether the mechanisms allowing movement generation were qualitatively similar in the PD patients and the control subjects, a general description of the characteristics of the movements performed by these two groups of subjects was first performed (one could not reject a priori the existence of a specific control strategy in the PD group such as, for instance, the generation of multiple discrete submovements to compensate for a major deficit in the coding of movement force; (Hallett and Khoshbin 1980). The main parameters involved in this first general analysis were: Reaction time, Movement duration, Peak hand velocity and Time to peak hand velocity. The last parameter was determined as a percentage of the total movement duration. This information was critical to determine whether there was a difference in the acceleration to deceleration ratio between the patients and the controls. As will be shown in the Discussion, such a difference would favor the idea that feedback loops are responsible for the movement hypometria observed in the PD patients. In parallel to these kinematic markers, the movement straightness was also determined. For each individual trial, the equation of the straight line (*l*) joining the start and end points was computed. The largest deviation (*d*) of arm trajectory from that line was computed. Movement straightness was defined as the largest deviation (*d*) of arm trajectory from *l*. Since path curvature is likely to increase with movement amplitude, movement straightness was also determined after normalization for this factor. Normalized straightness was defined as the ratio of *d* to the length of *l* (Atkeson and Hollerbach 1985). This parameter was important to identify potential deficits in on-line motor control.

End-point errors

End-point errors were the main parameter through which our key hypothesis was addressed, namely that the BG are critical for the planning movement amplitude (or of some covariate). Our main goal was thus to test whether PD patients exhibited a specific impairment in movement extent or whether they showed a mixed deficit. To address this question, end-point errors were expressed in a spherical frame of reference as amplitude and direction errors. Amplitude errors were defined as the difference between the actual movement amplitude (norm of the vector joining the hand starting point to the movement end-point) and the required movement amplitude (norm of the vector joining the hand starting point to the target). Direction errors were defined in the same way as the angular difference between the actual movement direction (eccentricity of the movement end-point) and the required movement direction (eccentricity of the target).

As emphasized in the Introduction, the statistical analyses carried out to identify significant differences in end-point errors between the Parkinson patients and control subjects could not be used directly to determine whether movement gain was selectively impaired in PD patients. To address this issue, a necessary step was to remove the part of the final error that was related to systematic biases in the estimation of the initial hand location. The detail of the procedure allowing this removal has been validated in a previous publication (Vindras et al. 1998). In brief, numerous studies have shown that bidimensional reaching movements are defined in a hand-centered coordinate system with an organizing mechanism

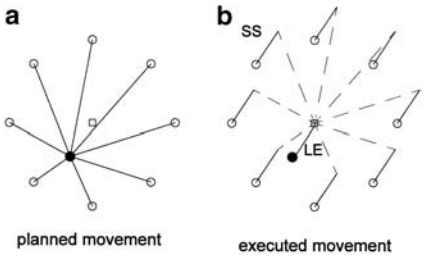

Fig. 2 **a** As shown in numerous studies, bidimensional movements are planned to follow a roughly straight line path (*continuous lines*) between the estimated hand initial location (*black circle*) and the target location (*white circles*). **b** The movements (*dashed lines*) are generated from the actual hand location (*white square*) leading to systematic end-point shifts (SS, *continuous lines*). SS is the exact vectorial opposite of the localization error vector (*LE*) from the actual to the estimated hand initial location

intended to move the effector along a straight-line path (Desmurget et al. 1997, 1999; Gordon et al. 1994; Morasso 1981; Vindras and Viviani 1998; for a review, Desmurget et al. 1998). As a consequence, an erroneous estimation of the hand location leads to a systematic shift (SS) of the end-point distribution (Fig. 2). Computationally, when targets are symmetrically arranged around the starting point, the systematic amplitude and direction errors on opposite targets nullify each other, and SS is approximately equal to the vectorial opposite of the localization error vector (LE) from the actual to the estimated initial hand location (LE=−SS). This equivalence provides us with a way to reverse the causal flow and to remove LE. The method allowing this reversal can be segmented in three stages (Vindras et al. 1998). First, the unique translation vector LE of all movement end-points that minimizes the mean quadratic error of a subject with respect to the corresponding targets is determined. This is equivalent to defining the virtual point from which the movement was planned. Second, all individual end-points are translated by LE. This is equivalent to removing systematic biases associated with the erroneous estimation of the initial hand location. Third, new amplitude and direction errors are computed.

In addition to constant end-point errors, variable errors were also computed for each condition, each subject, and each target location (10 repetitions). This parameter was defined as the 95% confidence ellipse of the end-point scatter (i.e., as the area within which 95% of the pointing of the subject should fall). The lengths and orientations of the axes of the confidence ellipses were defined from the eigenvalues and eigenvectors of the variance–covariance matrix of the end-point distributions (Johnson and Wichern 1982). Three main parameters were extracted from the variable error: (1) the surface area of the confidence ellipse (SURF); (2) the orientation of the confidence ellipse (AMA). This parameter was defined as the angle between the major axis of the ellipse and the mean movement direction (defined as the line connecting the starting point to the mean end-point); (3) the length of the major (LMA) and minor axis (LmA) of the confidence ellipse. The latter parameters were computed to determine whether a potential increase in the surface area of the confidence ellipse could be related specifically to one of the axis of the ellipse, or more exactly to one of the dimensions of the movement (extent versus direction). This idea was formulated on the basis of previous experiments suggesting on the one hand that the BG were critical for monitoring movement amplitude (see above) and on the other hand that the major axis of the confidence ellipse was generally closely aligned with the movement direction for planar reaching (Desmurget et al. 1997, 1999; Gordon et al. 1994; Vindras and Viviani 1998). In this case, the major axis of the confidence ellipse represents extent variability. The minor axis, which is orthogonal to the major axis, represents directional variability.

Results

Main movement characteristics

At a kinematic level, the main differences between the movements performed by the PD patients and the control subjects can be summarized by saying that PD patients exhibited: (1) longer reaction times (mean ± SD: PD, 682±188 ms; controls, 471±90 ms; $F_{1,\ 22}$=17.8, P<0.0005); (2) longer movement durations (PD, 732± 144 ms; controls, 588±112 ms; $F_{1,\ 22}$=10.7, P<0.005); (3) reduced peak velocity (PD, 391±124 mm/s; controls, 648±180 mm/s; $F_{1,\ 22}$=18.4, P<0.0005). No significant difference was observed for the acceleration-to-deceleration ratio between the patients and the control subjects (PD, 47±7%; controls, 48±7%; $F_{1,\ 22}$=0.3, P>0.60).

As displayed in Fig. 3, both the PD patients and the control subjects exhibited roughly straight hand paths. Movement curvature was slightly more pronounced in the control subjects than in the PD patients (PD, 5.6±2.3 mm; controls, 7.3±3.6 mm; $F_{1,\ 22}$=5.0, P<0.04). This effect was, however, mainly related to difference in the movement amplitude as shown by the fact that movement curvature was no longer affected by the group factor after normalization for movement amplitude (PD, 0.041± 0.015; controls, 0.045±0.025; $F_{1,\ 22}$=0.9, P>0.35).

In summary, these results indicate that reaching movements performed by the PD patients and the controls subjects were similar from a morphological point of view (acceleration-to-deceleration ratio; straightness), ruling out the hypothesis that movement generation relied on fundamentally different planning strategies in these two groups.

Systematic errors

Raw data and localization errors

A significant group by target interaction was observed for both the amplitude ($F_{7,\ 154}$=4.0, P<0.02) and the direction errors ($F_{7,\ 154}$=4.4, P<0.01) suggesting that: (1) there were significant differences in reaching accuracy between the PD patients and the control subjects; (2) these differences were not equivalent for all movement directions. These points are illustrated in Fig. 4. The left panel displays the mean reaching errors for the control subjects. The existence of a systematic upward shift of the end point distribution can be seen. As emphasized in the methods,

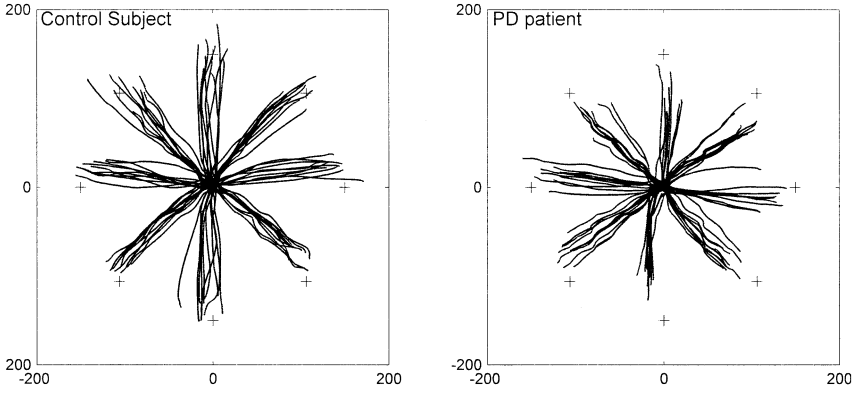

Fig. 3 Individual hand paths performed for movements to targets in eight directions (*black crosses*) by one control subject (*left panel*) and a Parkinson's disease (*PD*) patient (*right panel*). All movements begin from a central starting position and are directed outwards. Axis scale is in millimeters

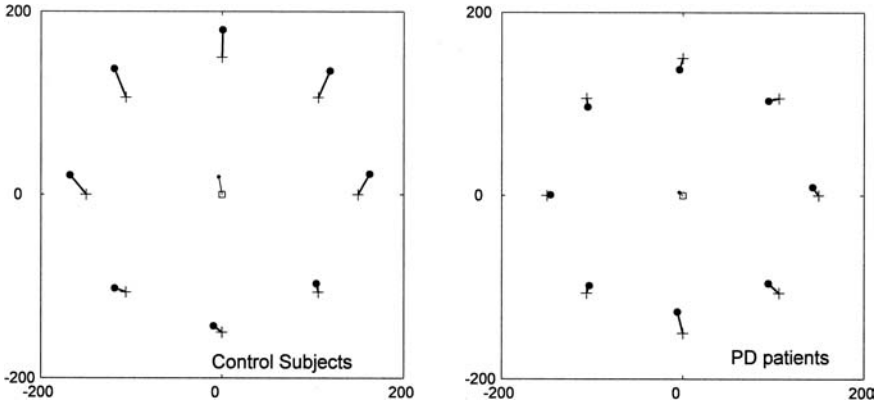

Fig. 4 Mean vector errors (*thick continuous line*) joining each target (*crosses*) to the corresponding movement end-point (*large black dots*). The systematic error averaged across targets is shown as a vector (*thin continuous line*) from the hand starting point (*white square*). *Left panel* displays data for the control subjects. *Right panel* displays data for the PD patients. Axis scale is in millimeters

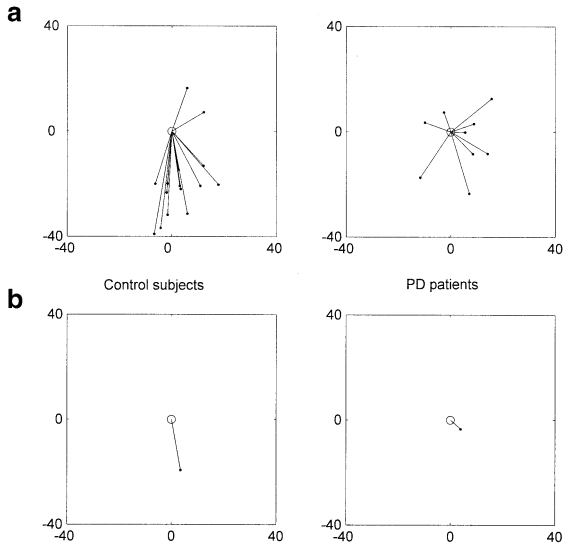

Fig. 5 **a** The mean bias in the estimation of the hand location, for each subject, as a vector (*continuous line*) originating from the starting position (*white circle*). **b** The mean bias in the estimation of the hand location averaged for all subjects. *Left column* displays data for the control subjects. *Right column* displays data for the PD patients. Axis scale is in millimeters

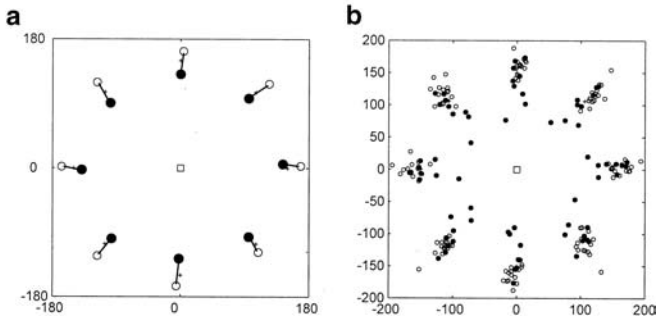

Fig. 6 **a** Mean movement end-point for the PD patients (*black circles*) and the control subjects (*white circles*). The movement starting point is represented by the *central white square*. The target location is represented by a *black cross*. Axis scale is in millimeters. **b** Mean movement end-point for each subjects. Same conventions as *left panel*

this shift is compatible with the idea that control subjects estimated that their hand was closer to the body than it actually was. In agreement with this view, the estimated localization errors were found to be directed toward the body in a majority of control subjects (13 of 15; Fig. 5, top row, first column). As a consequence, a systematic trend toward body-directed localization errors can be observed across the population of subjects (Fig. 5, bottom row, first column).

The right panel of the Fig. 4 shows the pattern of final errors for the PD patients. In this case, a marginal systematic shift of the end-point distribution was detected. For the PD group, the mean end-point error vectors presented mainly a centrifugal orientation, indicating the existence of a systematic underestimation of the movement gain. The absence of a systematic end-point shift in the PD population suggests that localization errors were not consistent within that group. In agreement with this view, the estimated localization errors were found to exhibit a large subject-to-subject directional dispersion (Fig. 5, top row, second column). In this case, individual errors "cancel" each other when individual data are averaged together, and no systematic localization error vector is observed at the population level (Fig. 5, bottom row, second column). It is important to note that the small size of the errors observed in Fig. 4 for the PD patients is partially misleading. As will be shown below, because of the variable direction of systematic errors in PD, averaging the data across subjects tended to reduce dramatically the magnitude of the errors existing at the individual level.

Removing localization errors

When localization errors are removed on an individual subject basis, the pattern of final end-point errors still exhibits significant differences between groups. This result is illustrated in Fig. 6 (left panel), which displays mean translated movement end-point for the PD patients (black circles) and the control subjects (white circles). The line connecting the mean movement end-point reached by the PD patients and the control subjects is oriented centripetally for all movement directions. This indicates that direction errors were similar in PD patients and control subjects, while amplitude errors was notably different between groups. The absence of substantial variations of the length of the line connecting the mean movement end-point reached by the PD patients and the control subjects as a function of the target location also suggests that the difference observed for amplitude errors between the PD patients and the control subjects were similar irrespective of the movement direction. These graphical observations are supported by statistical analyses showing that only amplitude errors depended on the group factor (direction errors: PD, 0.8±5.3°; controls, −0.72±3.9°; $F_{1,\ 22}$=1.7, P>0.20; amplitude errors: PD, −9.7±26 mm; controls, 14.7±16; $F_{1,\ 22}$=9.0, P<0.01). Both amplitude and direction errors were affected by the target factor, but these directional variations were similar for the control subjects and the PD patients (nonsignificant group-by-target interaction; $F_{7,\ 154}$=1.8, P>0.10). It is worth mentioning that the absence of significant variation of the mean direction error as a function of the group factor was not an artifact related to a higher directional variability in the PD population. As illustrated in Fig. 6 (right panel), the directional spread of the individual end-points around the target was comparable in both populations (PD, SD=5.3°; controls, SD=3.9°; Levene's HOV test, P>0.20).

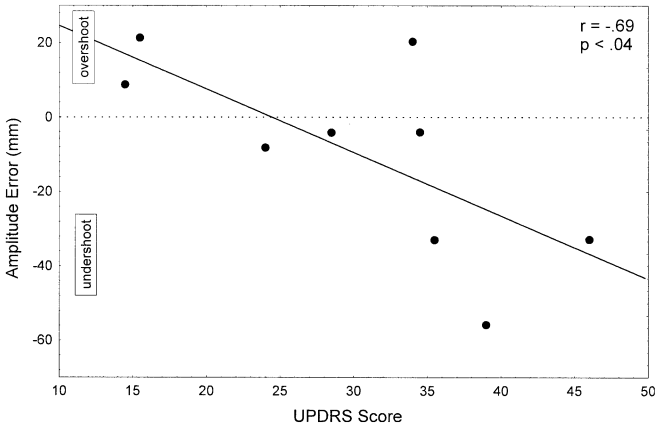

Fig. 7 Relationship between the mean amplitude error and the subject Unified Parkinson's Disease Rating Scale (*UPDRS*) score. The *dashed line* symbolize zero error. A point above this line indicates a target overshoot while a point below this line symbolizes a target undershoot. The significant correlation linking UPDRS scores and amplitude errors shows that the patients who presented with higher UPDRS score (i.e., a more severe stage of the disease) had a greater tendency to undershoot the target

Correlation analyses

Additional analyses were conducted to investigate the origin of the extent errors observed in the PD population. In the first analysis, we tested whether the magnitude of undershoot exhibited by the patients varied with their clinical state. To this end, the amplitude errors (after removals of localization errors) were correlated with the severity of the disease as measured by the UPDRS motor score. A negative significant correlation was found, indicating that the tendency to undershoot the target increased with the UPDRS score (r=–.69; P<0.04; Fig. 7). No similar trend was observed for direction errors (r=–0.28; P>0.45). In the second analysis, we tested whether the magnitude of movement undershoot was related to the age of the subjects. Even if the mean age was not significantly different in the PD and control groups, the patients were slightly older than the controls (61 versus 55 years; see Methods). Results failed to reveal any significant correlation between the amplitude errors and the age of the subjects in either the control (r=–0.05; P>0.85) or the PD group (r=–0.20; P>0.60). In the third analysis, we tested whether there was a relation between localization errors and the magnitude of movement undershoot. To this end, the amplitude errors were correlated with the components of the localization errors. The rationale for doing this test was based on the idea that localization errors reflected mainly a deficit in proprioception. Showing that the subjects who presented with the largest undershoot also presented with the largest localization errors would suggest that amplitude errors were associated with an impaired use of sensory reafference. Statistical analyses failed to support this view. No significant correlation was found between the amplitude errors and the components of localization error vectors in either the control subjects (r_{max}=0.31; P>0.25) or the PD patients (r_{max}=0.47; P>0.15).

In summary, the results presented in this section indicate that both the PD patients and the control subjects exhibit systematic biases in their ability to estimate the movement starting location. These biases are consistent within the control group, but exhibit large individual differences in the PD population. When systematic errors in the estimation of the initial hand location are removed, reaching errors appear to be related specifically to an erroneous specification of movement amplitude in the PD patients. Movement direction is controlled with equal accuracy in both groups.

Variable errors

Movement end-points were more scattered in the PD patients than in the control subjects. On average, the surface area of the end-point confidence ellipse was increased by nearly 32% in the former population (PD, 2,874±1,817 mm^2; controls, 2,170±1,254 mm2; $F_{1, 22}$= 4.4, P<0.05). Interestingly, this increase was not homogeneous, but was instead oriented mainly along the direction of movement. This was shown by a detailed examination of the characteristics of the end-point confidence ellipse. In both the PD patients and the control subjects, the end-point confidence ellipse had an elongated shape, with the major axis typically aligned with the mean movement direction (Fig. 8). On average, the angle between the movement direction and the direction of the major axis of the confidence ellipse was not significantly different in the PD patients and the control subjects (PD, –0.3±10°; controls, 1.9±7°; $F_{1, 22}$= 2.3, P>0.10). The same statistical identity was observed for the length of the minor axis of the confidence ellipse, indicating that directional variability was not noticeably increased in the PD patients with respect to the control subjects (PD, 39±14 mm; controls, 35±13 mm; $F_{1, 22}$=1.4, P>0.25). This was not the same for extent variability (i.e., for variability observed along the direction of movement). As shown by statistical analysis, the major axis of the confidence ellipse was significantly longer in the PD patients than in the control subjects (PD, 90±35 mm; controls, 75±26 mm; $F_{1, 22}$=6.7, P<0.02). This increase was present for all targets. This point is illustrated in Fig. 8. Note that there was a trend for the increase in extent variability to be modulated by the movement direction. This effect was, however, not significant (group by target interaction: $F_{7, 154}$=2.1; P>0.8). No significant relation could be found between the length of the major axis of the confidence ellipse and the UPDRS motor score (r=–0.034; P>0.35).

In summary, the results presented in this section indicate that PD patients presented an increase in extent variability without concomitant augmentation of the direction variability.

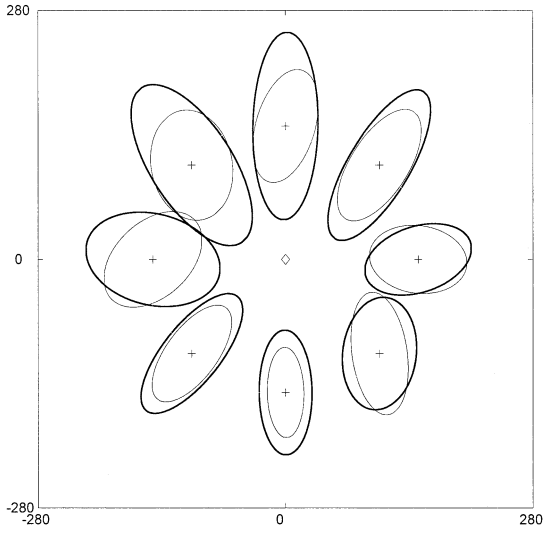

Fig. 8 Ninety-five percent confidence ellipses for the two experimental groups (control subjects: *thin lines*; PD, *thick lines*). Ellipses were computed, for each target eccentricity, after normalization of the individual data for direction and amplitude. The normalization procedure was as follows: (1) for each subject and each target location the mean of the end-point population (10 movements) was defined; (2) the angle α between the target direction and the line joining the hand starting-point (x=0; y=0) to the mean end-point was computed; (3) all the individual points of the scatter were rotated by α aligning the movement with the target direction; (4) the mean end-point of the rotated scatter was translated to be coincident with the target location (*black crosses*). The *central diamond* symbolizes the hand starting location. Axis scale is in millimeters

Discussion

There are three main findings in this experiment. First, localization errors due to an erroneous estimation of the initial hand location are different in the patients and in the controls. Second, when the confounding effect of initial localization errors is removed, the amplitude errors are increased in the patients with respect to the controls, without alteration of the direction errors. Third, movement extent variability is increased in the patients with respect to the controls, without a concomitant increase in movement variability. The meaning and implications of these results are discussed below.

Localization errors are different in the PD patients and the control subjects

Earlier studies in normal subjects have shown that the ability to estimate the static hand location was biased, even when vision was present. This bias was often reported to be oriented toward the body (Desmurget et al. 1999, 2000; van Beers et al. 1998; Wann and Ibrahim 1992). A similar trend was observed in the present study, but only for the control subjects. In PD patients, localization errors were more idiosyncratic. This result may account for some contradictory results reported in the literature (see Introduction). At a basic level, the greater variability observed in the PD population may be related to a defect in kinesthesia. Indeed, the process of localizing the hand at rest involves proprioception, a sense that has been repeatedly shown to be altered in PD patients (Demirci et al. 1997; Jobst et al. 1997; Klockgether et al. 1995; Schneider et al. 1987; Zia et al. 2000). At a second level, it is also possible that the more variable performance exhibited by the patients is reflective of a more general deficit in sensorimotor integration. Our protocol allowed vision of the hand prior to movement onset, mainly to prevent a potential drift in proprioception (Wann and Ibrahim 1992) and to minimize the magnitude of localization errors (Desmurget et al. 1999; Vindras et al. 1998). When vision and proprioception are present, the nervous system is known to combine these different signals to estimate the initial hand location (Rossetti et al. 1995; van Beers et al. 1996, 1998). This "integrative" operation might be altered in PD patients who have been shown to have difficulties integrating a proprioceptive signal with a concurrent or remembered visual signal (Adamovich et al. 2001).

Movement amplitude is selectively affected in PD patients

After subtraction of the systematic errors related to an erroneous estimation of the initial hand location, only the adjustment of movement amplitude was found to be defective in PD patients. While the controls tended to overshoot the target, the patients tended to undershoot it. This effect was present and of similar magnitude for all movement directions. On average, movement gain was reduced by 15% in the patients with respect to the controls. Interestingly, a significant correlation was found, in the PD patients, between the level of undershoot and the severity of the disease: the patients presenting with higher UPDRS motor scores exhibited a greater tendency to undershoot the target. This strongly reinforces the hypothesis that errors in movement gain result effectively from a dysfunction within the BG network. Additional evidence supporting this view is provided by the selective increase in movement extent variability in the patient population. No significant increase was observed for the movement direction variability.

With respect to these results, it is worth noting, however, that the selective deficit observed in the control of movement amplitude does not indicate definitive and exclusive central representations of either movement direction or movement amplitude. It is virtually ensured that other aspects of the movement covary systematically with these two parameters. For instance, common covariates of changes in movement extent include changes in peak velocity, movement accuracy, joint torques, and muscle EMG. The present experiments do not provide a way to dissociate these possible covariates. However, our results support the idea that different functional channels are involved in the control of

movement direction (and covariates) and movement extent (and covariates), a hypothesis that has been proposed repeatedly from psychophysical results (see below).

From these observations, the question arises about the functional origin of the hypometria exhibited by the PD patients. This issue is addressed below.

Movement hypometria and on-line feedback loops

At a first level, the hypometria exhibited by the PD patients can reflect a dysfunction of the feedback loops allowing control of the movement during its time course (Lawrence 2000). The most direct evidence favoring this view was recently provided by Smith et al. (2000). These authors instructed patients with Huntington's disease (in which early cell loss is restricted largely to the striatum) to point from a central position to one of eight targets located on a surrounding circle. As shown by behavioral recordings, these patients were unable to correct self-generated initial errors in movement trajectory. Corrective responses to externally generated force pulses triggered at the beginning of the movement were also grossly abnormal. To explain these findings, Smith et al. proposed that the sensory signal is biased when the BG are damaged. According to this view, the BG dysfunction leads to the transmission of an erroneous proprioceptive signal toward the functional module that mediates feedback correction. Electrophysiological observation support this view by showing that passive limb movements activate the BG neurons (Crutcher and Delong 1984; DeLong et al. 1985; Hamada et al. 1990) and generate abnormal (exaggerated) sensory responses in the pallidal neurons of parkinsonian monkeys (Filion et al. 1988). This impaired responsiveness of the BG neurons to peripheral input could lead to an overestimation of the distance covered by the hand, and thus hypometria. This hypothesis fits well with several experimental observations showing that dynamic proprioception is impaired in PD patients in such a way that the distance covered by the arm is overestimated (Demirci et al. 1997; Jobst et al. 1997; Klockgether et al. 1995; Moore 1987; Zia et al. 2000).

In spite of the previous evidence, the ability of a feedback deficit to account for the pattern of errors reported in the present study seems unlikely. Indeed, on-line feedback loops making use of proprioception are not only important for controlling movement extent (Goodale et al. 1986; Pélisson et al. 1986). They are also critical for modulating movement direction (Desmurget et al. 1999, 2001; Prablanc and Martin 1992). Since proprioception is a global signal that does not segregate between amplitude and direction, it is not clear why a feedback-related deficit should affect selectively movement extent. With respect to this conclusion, one may also underline our failure to identify a significant relation, in the PD group, between the movement undershoot and the proprioceptively related localization errors, as would be expected if the amplitude errors exhibited by the patients were associated with an impaired use of sensory reafference.

The ability of a feedback-related deficit to account for our data is also challenged by kinematic observations showing that the temporal organization of the movement was not affected in PD patients. Theoretically, one may predict that the temporal profile of the trajectory should be influenced if the movement is stopped earlier than initially planned because of an overestimation of the distance traveled by the arm. In this case, the time to peak velocity should occur later in percentage of the total movement duration. This prediction is not supported by our experimental observations, which failed to indicate any modification of the acceleration-to-deceleration ratio in the PD group.

A last argument challenging the idea that a feedback-related deficit may account for the pattern of error observed in the present study comes from converging behavioral data suggesting that the estimation of the current hand location during reaching movements is based mainly on the efferent signal. Of course, there is no doubt that externally generated proprioceptive disturbance arising, for instance, in vibration experiments (Redon et al. 1991) or when a force is added to the ongoing movement (Bhushan and Shadmehr 1999; Smith et al. 2000; Won and Hogan 1995) leads to significant modifications of the motor response. However, there is little evidence that proprioceptive input is able to influence the dynamic estimation of the hand location, in the context of normal reaching movements.

A first argument suggesting that the estimation of the current hand location is mainly based on the efferent signal was provided by Bard and colleagues (Bard et al. 1999). These authors instructed a deafferented patient to look and point to visual targets displayed in the peripheral visual field. Vision of the moving limb was not allowed. In some trials the target location changed slightly during the course of the ocular saccade. Because of saccadic suppression, this manipulation was not consciously detected by the patient, who was convinced that she pointed to a stationary target. Results showed that she was able to correct her movement on-line to reach the new target location despite the absence of peripheral information. Strikingly, the accuracy of her corrections was not significantly different from that of control subjects. Additional evidence supporting the critical contribution of nonsensory feedback loops to on-line movement guidance was provided by behavioral studies showing that hand trajectory could be amended with a shorter latency than the minimal latency required to process peripheral information (Higgins and Angel 1970). In agreement with this conclusion, Jaeger et al. (1979) showed that altering the proprioceptive signal through tendon vibration did not modify the corrective reaction time observed in response to a visual perturbation.

More direct evidence pleading for a limited contribution of the dynamic proprioceptive signal to the estimation of the hand location in the context of reaching movement comes from "perturbation" experiments in

which an artificial mismatch between vision and proprioception is introduced prior to movement onset (Jaric et al. 1992; Sainburg et al. 2003). For instance, Rossetti et al. (1995) instructed human subjects to point toward visual targets without visual reafference from their moving hand. Two conditions were considered. In the first condition, the pointing fingertip was viewed through prisms that created a substantial visual displacement (5 cm), while the target was presented outside the shifted field and thus was normally seen (no shift). In the second condition, both the index fingertip and the target were seen normally, i.e., the relationship between the hand and the target was not altered. Comparison between these two conditions showed that the visual shift of the fingertip position prior to movement caused the initial movement direction to be systematically and persistently biased (planning error). This shift was strictly proportional to the shift detected in the final end-point error. Such an identity indicates that the existence of a substantial mismatch between the estimated (motor outflow) and sensed (proprioceptive input) hand position did not cause the current trajectory to be corrected. This conclusion is compatible with other data showing that reaching errors tend to accumulate in sequential pointing movements, suggesting that proprioception is not able to reset a bias in state estimation during the ongoing action (Bock et al. 1990; Bock and Arnold 1993; Bock and Eckmiller 1986). It also fits well with computational studies showing that models ignoring totally the potential contribution of on-line feedback loops to movement control are remarkably successful at capturing the main characteristics of the movements final errors recorded during visually directed movements (Carrozzo et al. 1999; Flanders et al. 1992; Gordon et al. 1994; McIntyre et al. 2000; Vindras et al. 1998; Vindras and Viviani 1998).

Movement hypometria as a planning deficit

In healthy individuals, fast reaching movements involve typically three bursts of EMG activity (Jeannerod 1988; Berardelli et al. 1996, for reviews): (1) a first burst in the agonist muscles accelerates the movement. The size of this initial burst is scaled with the amplitude and velocity of the movement; (2) a second burst in the antagonist muscles decelerates the movement; (3) a third small burst in the agonist muscles stabilizes the limb at the target position. As initially shown by Hallett and Khoshbin (Hallett and Khoshbin 1980), this typical triphasic pattern is altered in PD patients. When these patients are required to perform large reaching movements, the first agonist burst is often insufficient, leading to the occurrence of repeated cycles of alternating agonist and antagonist activity. Interestingly, the downward scaling of the initial EMG burst does not seem to be related to a ceiling effect for PD patients, i.e., to the inability to "energize" the agonist muscles. It seems rather related to an inability to properly scale the force to be generated as a function of the distance to be covered. This was initially demonstrated by behavioral data showing that parkinsonian subjects were able to produce larger bursts of EMG activity than the ones observed during large reaching movements (Berardelli et al. 1986), especially when accuracy demands were minimized (Phillips et al. 1994; Sanes 1985; Sheridan and Flowers 1990; Teasdale et al. 1990).

The inability of PD patients to scale the magnitude of the initial EMG response with respect to the required movement amplitude has led many authors to assume a direct contribution of the BG network to the planning of movement force (or extent). In agreement with this view, single-unit recording studies have identified amplitude/velocity effects in a majority of pallidal neurons, in monkeys (Georgopoulos et al. 1983; Turner and Anderson 1997). The significance of this observation was, however, questioned in subsequent studies showing: (1) that the activity of a given neuron was never "pure" but modulated by other motor parameters, such as the required precision or the movement direction; (2) the relation between pallidal discharge and movement parameters was weak and inconsistent across different task conditions (Brotchie et al. 1991; Mink and Thach 1991). Another challenge was found in the observation that movement-related activity in the motor portions of the BG begins predominantly after the response recorded in both the motor cortex (Alexander and Crutcher 1990) and the arm muscles (Anderson and Turner 1991; Mink and Thach 1991; Nambu et al. 1990).

In light of the previous observation, the idea that the BG are directly involved in the process of movement planning was sometimes rejected (Wichmann and DeLong 1996). However, one may argue that the inconclusive results reported in the literature, up to now, are not totally decisive. Regarding the "timing" issue, one may notice, for instance, that some BG neuronal activity occurs early in a movement (Georgopoulos et al. 1983). This suggests that differences in recording location may be an important parameter. Regarding the lack of pure extent-related activity, one may argue that the absence of a clear signal is caused by the fact that movement amplitude results from the combined activity of several cerebral areas, including, in addition to the BG, the motor cortex and the cerebellum.

In agreement with the previous reservations, it is worth noting that clear activations of the BG network have been reported, during movement preparation, in imaging experiments (Deiber et al. 1996). This was the case in a recent study carried out by our group and in which a precue paradigm was used. We found that a condition that emphasized movement extent planning (an amplitude precue was presented prior to movement onset) resulted in enhanced activation of the BG structures in comparison with conditions that emphasized movement direction planning (direction precue) or no planning (no precue). Similar variations of the neural activity in the BG as a function of the movement extended and/or velocity have been observed in other studies (Turner et al. 1998; Siebner et al. 2001).

If the BG network is involved in movement planning, it remains to be understood how a dysfunction within this structure can cause movement to be biased toward selective undershooting and an exclusive increase in extent variability. One possibility is that that the activity of all arm muscles is biased in a similar proportion during the movement. In other words, the typical pattern of error observed in this experiment can be easily explained by assuming that a brake affects homogeneously all the motor commands sent to all muscles (Vindras and Viviani 1998). This idea is compatible with the observation that, in PD patients, movements are often performed with normally timed EMG bursts, but the amount of EMG activity is underscaled relative to the desired movement parameters (Berardelli et al. 1986, 2001; Pfann et al. 2001; Godaux et al. 1992). It also fits well with the suggestion that a critical role of the BG network is to reinforce the cortical mechanisms that prepare the commands to move (for a review, Berardelli et al. 2001). It is tempting to speculate that a deficit in this boosting mechanism reduces homogenously the level of motor output, thus leading to hypometria. An alternative (but not necessary incompatible) hypothesis is that the tuning of spinal interneuronal systems may be disrupted during movement planning. Support to this idea can be found in observations showing that the control of spinal reflexes is abnormal in PD patients. In particular, recent data have demonstrated in PD patients: (1) that movement-related inhibition of antagonist motor neurons by disynaptic Ia reciprocal inhibition is altered (Meunier et al. 2000); (2) that presynaptic inhibition of monosynaptic Ia terminals is reduced (Morita et al. 2000). These abnormalities are likely to affect movement amplitude by preventing an appropriate antagonist inhibition. Indeed, one may expect the impaired perimovement modulation of reciprocal Ia inhibition to undermine the descending motor command to agonist motoneuron pools, especially if antagonist muscles undergo a fast stretch. In parallel, one may also expect a facilitation of the antagonist burst to occur both directly, through an insufficient presynaptic inhibition of antagonist monosynaptic Ia terminals and indirectly, through an increased inhibition of the reciprocal Ia-inhibiting interneurons projecting on antagonist motoneurons. This combined action could result in a decrease in movement amplitude, without affecting movement direction. In contrast to this idea, however, recent data seem to indicate that although antagonist EMG activity may be increased in PD subjects during movement (Pfann et al. 2001), the increase is minor, not always observed, and thus unlikely to account, by itself, for the dramatic slowing and hypometria observed in PD (Pfann et al. 2001; Johnson et al. 1991).

The parametric model of motor control

The conclusion that the BG are directly involved in the planning of movement amplitude (or some covariate) could be of major importance for the debate about the control logic of the motor system in executing goal-directed movements. During recent decades, it has been suggested that motor planning was a parametric process involving an independent specification of the Cartesian amplitude and Cartesian direction. According to this idea, reaching movements of different amplitudes and speed performed in the same direction are achieved by simply scaling the magnitude of the EMG bursts without modifying the global pattern of muscle contraction. Data supporting this view are manifold. Reaction times are reduced by prior information about either the direction or the distance of the target with respect to the hand (Bock and Arnold 1992; Bock and Eversheim 2000; Rosenbaum 1980). Movement extent and direction are specified separately during planar movements (Favilla et al. 1989; Ghez et al. 1997). Changes of the visuomotor gain are learnt more easily than changes in movement direction and generalize to movements in all directions (Bock 1992; Krakauer et al. 2000; Pine et al. 1996; Vindras and Viviani 2002). When subjects point to targets symmetrically distributed around a starting position, their average error is strongly correlated with their errors in localizing their unseen hand on the starting position, as should be the case for processes based on the hand-target vector (Desmurget et al. 1999; Vindras et al. 1998). In pointing to nonmemorized visual targets, the direction and extent variability are independent (Desmurget et al. 1997, 1999; Gordon et al. 1994; Messier and Kalaska 1997; Vindras and Viviani 1998). In monkeys, the direction of the hand–target vector is correlated to the neuronal activity in many cortical and cerebellar areas (for a review, Georgopoulos 1995; Kalaska and Crammond 1992). The observed correlations are generally so robust that the movement spatial direction can be derived directly from neuronal activity using appropriate algorithms (Georgopoulos 1995). The results of the present study generalize these observations in two ways: First, we confirm that movement amplitude can be biased selectively, without alteration of the movement direction. Second, we link the control of movement gain to the BG network. This second point is important. Indeed, there is no clear neural correlate for movement extent (Vindras and Viviani 2002), and this absence has often been considered a major weakness of the parametric conception of motor control (for a review, Desmurget et al. 1998).

In summary, the present study provides support to the hypothesis that the BG are specifically involved in the planning of movement amplitude (or of some covariates) and that this involvement leads the PD patients to significantly undershoot the target during visually directed movements performed without vision of the limb. Although the exact contribution of the BG to the control of movement extent has not yet been elucidated, we suggest that this structure participates in extent planning by modulating cortical activity and/or the tuning of the spinal interneuronal systems.

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