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The basal ganglia network mediates the planning of movement amplitude

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Abstract

This study addresses the hypothesis that the basal ganglia (BG) are involved specifically in the planning of movement amplitude (or covariates). Although often advanced, based on observations that Parkinson's disease (PD) patients exhibit hypokinesia in the absence of significant directional errors, this hypothesis has been challenged by a recent alternative, that parkinsonian hypometria could be caused by dysfunction of on-line feedback loops. To re-evaluate this issue, we conducted two successive experiments. In the first experiment we assumed that if BG are involved in extent planning then PD patients (who exhibit a major dysfunction within the BG network) should exhibit a preserved ability to use a direction precue with respect to normals, but an impaired ability to use an amplitude precue. Results were compatible with this prediction. Because this evidence did not prove conclusively that the BG is involved in amplitude planning (functional deficits are not restricted to the BG network in PD), a second experiment was conducted using positron emission tomography (PET). We hypothesized that if the BG is important for planning movement amplitude, a task requiring increased amplitude planning should produce increased activation in the BG network. In agreement with this prediction, we observed enhanced activation of BG structures under a precue condition that emphasized extent planning in comparison with conditions that emphasized direction planning or no planning. Considered together, our results are consistent with the idea that BG is directly involved in the planning of movement amplitude or of factors that covary with that parameter.

Introduction

It is often suggested that the basal ganglia (BG) are involved in the control of movement amplitude (or covariates, e.g. velocity, torques, muscle EMG, movement duration). This idea, based initially on the observation that Parkinson's disease (PD) patients exhibit hypokinesia (Denny-Brown, 1968; Berardelli *et al.*, 2001), has found support from psychophysics (Desmurget *et al.*, 2003), imaging (Turner *et al.*, 1998, 2003; Taniwaki *et al.*, 2003) and single-cell recording studies (Anderson & Turner, 1991; Georgopoulos *et al.*, 1983; Turner & Anderson, 1997).

Theoretically, the BG network could influence movement amplitude by mediating on-line feedback control processes (Lawrence, 2000; Smith *et al.*, 2000) and/or feedforward planning (Flowers, 1976; Berardelli *et al.*, 2001; Desmurget *et al.*, 2003). The aim of the present study is to test the second hypothesis using a precued Reaction Time (RT) paradigm. Changes in RT can reflect the time required for discrete aspects of motor planning independent of feedback control processes. Relevant here, precues for movement extent and direction can reduce RTs additively, implying thereby that movement direction and amplitude are planned separately (Rosenbaum, 1980; Lepine *et al.*, 1989;

Bock & Arnold, 1992). This idea is also supported by disparate additional observations: specification of extent and direction follows different timecourses (Ghez *et al.*, 1997); visuomotor gains are learnt more readily and generalize more widely than directional rotations (Krakauer *et al.*, 2000; Vindras & Viviani, 2002); learning of rotations and gains activates different cortical and subcortical networks (Krakauer *et al.*, 2004); and, direction and extent errors vary independently (Gordon *et al.*, 1994; Desmurget *et al.*, 1997; Vindras & Viviani, 1998; Desmurget *et al.*, 1999). This perspective should not be taken to imply that extent is controlled in isolation, but rather that, at certain stages of motor planning, a constellation of parameters related to the extent of movement are controlled independently from parameters related to movement direction.

The present study uses a precue paradigm to determine whether the BG network contributes specifically to the planning of movement extent. A first experiment investigated this question 'indirectly'. We assumed that if the BG is involved in extent planning then PD patients (who exhibit a major BG dysfunction) should exhibit impaired use of amplitude precues but a preserved ability to use direction precues. Alone, however, this result could reflect dysfunction of other CNS networks independent of, or secondary to, the abnormal BG outflow associated with PD. A second complementary experiment was thus designed to 'directly' test for selective involvement of the BG in extent planning. We investigated whether normal subjects exhibit greater activation of the BG when an amplitude precue is presented, relative to

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activations under direction- or null-precue conditions. To avoid ambiguity, it is worth mentioning that the two experiments reported here, although similar, are not strictly comparable because of slight differences in the experimental apparatus (e.g. seated in a chair vs. lying in the scanner) and the mean age of the subjects. These experiments are presented together because they use comparable paradigms and their results are mutually reinforcing.

Materials and methods

Subjects

For the behavioural study (psychophysics in PD), seven patients (two females and five males, mean \pm SD age 59 ± 8 years) and seven control subjects (three females and four males, age 54 ± 12 years) were selected, after their informed consent was obtained. Paper records containing the exact age of two control subjects were lost. When either the minimal or the maximal age value for these two subjects was chosen (range of ages was between 40 and 80 years old to participate in the study), the age difference between the two groups was not statistically significant ($t < 1.25$, $P > 0.20$). 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 or other neurologic disorders at enrolment. The patients enrolled in this study were at a severe stage of the disease and were under consideration for surgical treatment. The patients did not exhibit major signs of tremor. At the time of evaluation the patients had been off medication for more than 12 consecutive hours (patients were evaluated in the morning having been off medication since the previous evening). For each patient, the Hoehn and Yahr score was determined before the experiment. The scores ranged from 2 to 4.5 (mean 3.1 ± 0.8).

For the imaging study, 12 right-handed naive subjects (six females, six males) were selected. Their age ranged from 20 to 47 years (mean 32.4 ± 8.5 years). All subjects gave informed consent and the study was approved by the institutional Human Investigation Committee of Emory University. All subjects underwent a brief neurologic examination to ensure they were healthy and devoid of visual deficits.

Apparatus

A schematic representation of the experimental apparatus is presented in Fig. 1. It consisted of a 19-inch computer screen that was positioned in front of the subject at a distance of 45 cm. During the experiment, movement of an infrared emitting diode located on the subject's index fingertip was recorded with an OPTOTRAK/3020 system (Nothern

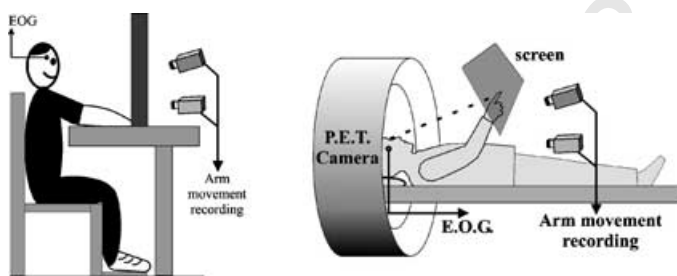


FIG. 1. (Left) Apparatus for the behavioural experiment. Subjects were seated in front of computer screen that was placed on a table. Their head was free to move. (Right) Apparatus for the imaging experiment. Subjects were supine in the scanner with the computer screen positioned in front of them, in a metallic frame. Their heads were immobilized with a thermoplastic mask. See text for details.

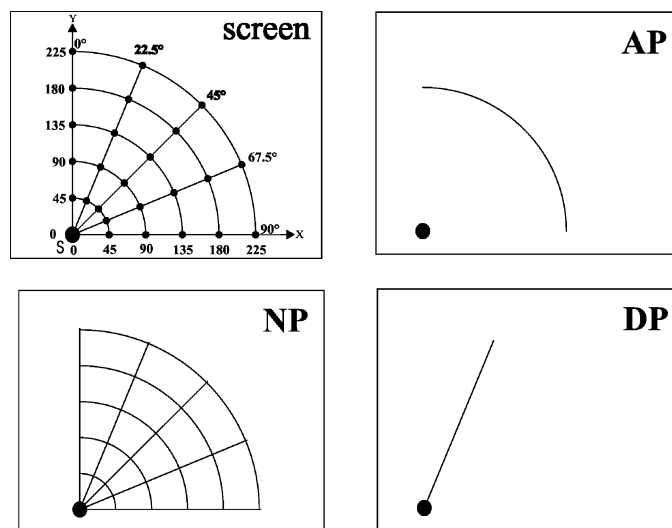


FIG. 2. Illustration of the location of the targets on the computer screen ('screen') and of the three precue screens (NP, no precue; AP, amplitude precue; DP, direction precue). S represents the hand starting location.

Digital Inc, Waterloo, Ontario, Canada) at a sampling frequency of 200 Hz.

Experimental conditions and procedure

The task was to point with the right hand 'as quickly and accurately as possible with a single uncorrected movement' to visual targets (white dots) presented on the computer screen. No special emphasis was put on movement velocity or on RT. Twenty-five targets were used in this experiment. As shown in Fig. 2, targets were positioned around five different circles having a common centre (S) and different radii of 45, 90, 135, 180 and 225 mm. Targets were located at 0, 22.5, 45, 67.5 and 90° on each circle (clockwise direction; targets directly above S on the vertical axis were at 0°; targets directly to the right of S on the horizontal axis were at 90°). The common centre and movement starting position (S, Fig. 2) was located at the left-bottom of the screen (small white circle). When expressed in visual angles eye movements ranged in the vertical and horizontal directions from 5.7 to 25.6°.

For the behavioural experiment a typical trial involved three steps. (i) The movement starting point was turned on for 1.5 s allowing the subject to position his/her index fingertip at the correct location (touching point S on the computer screen). (ii) The movement starting point was turned off while the 'precue screen' was turned on for 1 s plus a random delay ranging from 0 to 1 s. The subject was told not to 'scan' the precue screen with his/her eyes but to keep his gaze anchored on the index fingertip. Binocular DC electro-oculography displayed on an oscilloscope was used to monitor compliance with these instructions. (iii) The 'precue screen' was turned off and the actual target was presented for 1 s instructing the subject to initiate a reach to the target. The subject was allowed to move his/her eyes during reaching. (iv) After completion of the reaching movement, the target was turned off and the movement starting point was turned on again.

Three precueing conditions were used in both the behavioural and imaging parts of this study (Fig. 2).

Direction precue (DP)

The line passing through S and the target to be presented was displayed informing the subject about the direction of the upcoming movement.

Amplitude precue (AP)

The arc of circle centred on S and passing through the target to be presented was displayed informing the subject about the amplitude of the upcoming movement.

No precue (NP)

All lines and arcs passing through all the targets were displayed on the screen leaving the subject with no information about the exact amplitude or direction of the upcoming movement. Each experimental condition was presented in separate blocks (DP, AP, NP). Each block was composed of 25 trials and was repeated four times, leading to a total number of 12 sessions and 300 trials (12 sessions \times 25 trials). For the behavioural study, all 25 targets were randomly presented in each repetition of a given condition. The sequence of target presentations was strictly balanced between the experimental conditions. In addition, the different experimental blocks were randomly ordered.

For the imaging study, the procedure was identical except for one change. In only one half of the trials was the precue screen followed by presentation of a target (go task). In the remaining trials, the computer screen was blanked after the precue screen. In this case, the subject was instructed not to move his/her hand or gaze and to wait for the next precue screen (no-go task). Thus, on no-go trials only one movement component (amplitude or direction) was planned. As a consequence, movement direction was planned twice as often in DP (i.e. planned in both the go and no-go tasks) as in AP or NP (i.e. planned only in the go task). Likewise, movement amplitude was planned twice as often in AP as in DP and NP. If instead, every trial had been a 'go' trial (i.e. if an actual target was presented and a movement planned and executed), it is not clear whether activations related solely to the early encoding of movement amplitude or direction would have been detectable. The 'no-go' trials increased the contrast between conditions. For the imaging study, 13 go trials and 12 no-go trials were presented in each scan.

Analysis of behavioural data

The x , y and z position signals delivered by the Optotrack system 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 thresholds: hand velocity, 8 cm/s; hand acceleration, 150 cm/s² (these values were chosen to statistically fit with the values obtained from a visual inspection of the data). Because the PD patients tended to move more slowly than the control subjects, we tested, in the behavioural study, whether using a single threshold for both populations could bias the results. To this end we tested how lowering the thresholds in the PD group might affect the data (e.g. hand velocity 6 cm/s, hand acceleration 120 cm/s²). We also tested the effect of using a 'relative threshold' (e.g. 5% of the peak velocity). The outcome of these manipulations was marginal and without effect regarding the main results.

Three main motor parameters were analysed: reaction time (RT), movement duration (MD) and movement error. For the latter parameter, an orthogonal frame of reference was defined relative to the computer screen (Fig. 1). This frame was centred on the movement starting point S. The X -axis was in the computer screen plane and orientated rightward. The Y -axis was in the computer screen plane and orientated upward. The Z -axis was orthogonal to the computer screen and orientated toward the subject. Movement errors were expressed in a spherical frame of reference as amplitude and direction errors.

Amplitude errors (AE) were defined as the difference between the actual movement amplitude and the required movement amplitude. Direction errors (DE) were defined in the same way as the angular difference between the actual movement direction and the required movement direction.

For the behavioural study, a two-way between-within ANOVA was used to test the influence of experimental conditions on movement parameters. The two experimental factors were 'Group' (between factor: two levels, Parkinsonian vs. Control), and 'Precue' (within factor: three repeated levels, AP, DP, NP). For the imaging study, univariate ANOVA with repeated measures was performed (three repeated levels: AP, DP, NP). The data entered in the different ANOVAs were the means per condition and subject. Because the sphericity requirements were not likely to be met by our data with repeated measures, we carried out the Box adjustment procedure for degrees of freedom (Hays, 1988). The Geisser-Greenhouse estimate was used. Threshold for statistical significance was set at $P < 0.05$.

Imaging

Imaging methods have been described in previous publications (Desmurget *et al.*, 1998a, b; Turner *et al.*, 1998; Desmurget *et al.*, 2001). In brief, regional cerebral blood flow (rCBF) images were acquired with a Siemens ECAT Exact scanner, using a modified autoradiographic method in 3-D mode. Ninety-second scans were recorded every 8 min. The series of scans was made from each subject using bolus intravenous injections of H₂¹⁵O (25 mCi) delivered into the left arm 10 s before the start of the scan. Performance of the designated task began at the same time as the scanning. Images were reconstructed using calculated attenuation correction. [Q4]

Image processing was performed on a SUN Ultra 1 computer. For spatial normalization, a within-subject alignment of positron emission tomography (PET) scans was performed using an automated registration algorithm (Woods *et al.*, 1998a; Woods *et al.*, 1998b). For each subject, the mean PET image was then coregistered to a population-based PET reference atlas centred in Talairach coordinates (Talairach & Tournoux, 1988), using affine and nonlinear transforms with 60 degrees of freedom (Woods *et al.*, 1998a; Woods *et al.*, 1998b). Co-registered PET images were smoothed to a final isotropic resolution of 15 mm full width at half maximum and normalized to each other using proportionate global scaling.

A voxel-by-voxel analysis of variance (ANOVA) for a randomized complete block design was used for all contrasts, to identify significant task effects (Neter *et al.*, 1990; Woods *et al.*, 1996). The effects (and source of variance) in the statistical model were subject, task and repetition. Given the subjects' consistent task performance and the randomization procedure, repetition could be treated as replication, resulting in a two-way ANOVA (Turner *et al.*, 1998; Desmurget *et al.*, 2001). Because the present experiment is bounded by an explicit question, namely whether or not BG is selectively involved in the planning of movement amplitude, a planned approach was used for statistical analysis and the search volume was restricted to the BG complex. This planned approach favours sensitivity by removing the need for stringent adjustments for multiple comparisons. At the same time however, it precludes comprehensiveness by ignoring the potential role of other structures. The region of interest was drawn around the BG using an average of the spatially normalized high resolution structural MRI scans from all subjects as a template. The region included striatum, globus pallidus, thalamus and substantia nigra. The statistical threshold was set at $P < 0.01$. No correction for multiple comparisons was applied within this restricted volume of interest. Four contrasts were tested: (1) AP minus DP; (2) AP minus NP; (3) DP minus AP; (4) DP minus NP. [Q5]

Results

Behavioural data on PD patients and control subjects

Movement final accuracy was not affected by the group (AE, DE: $F_{1,12} < 3.9$, $P > 0.07$) or the precue factors ($F_{2,24} < 2.3$, $P > 0.10$) and no interaction was observed ($F_{2,24} < 2.1$, $P > 0.15$). This is not surprising considering that ambient vision allowed for on-line guidance of the hand toward the target (movement accuracy is normal in PD patients when vision of the moving hand is allowed; Flowers, 1975, 1976).

The duration of the movement did not vary as a function of the precue given to the subject prior to target presentation (AP, 376 ms; DP, 375 ms; NP, 371 ms; $F_{2,24} = 1.34$, $P > 0.25$). MD was only affected by the group factor ($F_{1,12} = 5.44$, $P < 0.04$). The PD patients took 24% more time to execute the movement than the control subjects (414 vs. 334 ms). No interaction was observed between the experimental factors ($F_{2,24} = 0.21$, $P > 0.75$) showing that the effect of the precue factor on MD was not statistically significant in the two subject groups.

The interacting effects on reaction time (RT) of group and precue type showed clear evidence that parkinsonian subjects were distinctly impaired at preplanning movement amplitude. RT was significantly longer in the patient group than in the control group (significant group effect: $F_{1,12} = 24.1$, $P < 0.0005$). In addition, a precue effect was observed for both the PD patients and the control subjects (significant precue effect: $F_{2,24} = 82.3$, $P < 0.0001$). Critically, the precue effect was not similar in the two groups, leading to a significant group \times precue interaction ($F_{2,24} = 9.7$, $P < 0.002$; Fig. 3. For the control subjects, RT was reduced by the same amount irrespective of the nature of the precue provided prior to movement onset. As shown by *post hoc* analyses, while RTs under the NP condition (295 ms) were significantly different from those under AP (252 ms; $P < 0.0002$) and DP (252 ms; $P < 0.0002$), the two latter conditions did not differ from each other ($P > 0.99$). For the PD patients, in contrast, RT was reduced by significantly different amounts when AP and DP precues were

provided prior to movement onset. This was shown by *post hoc* analyses indicating that although RTs under the NP condition (414 ms) were significantly different from those under AP (381 ms; $P < 0.0005$) and DP conditions (342 ms; $P < 0.0001$), there was also a significant difference between the effects of amplitude and direction precue types (AP and DP, $P < 0.0003$). Further analyses confirmed this fact by showing that the decrease in RT associated with DP (relative to NP) was similar in the two groups (PD, 17%; controls, 15%; $F_{1,12} = 0.8$, $P > 0.35$). By contrast, the RT decrease associated with AP was larger in the control group than in the PD group (PD, 8%; controls, 14%; $F_{1,12} = 6.2$, $P < 0.03$). The smaller reduction in RT under AP than under DP was very robust across parkinsonian subjects. As shown in Fig. 3, it was observed in all patients with no exception.

Although it is possible that the between-group difference in ability to use an AP precue could arise from group differences in attentional control, a separate analysis failed to support this hypothesis. It has been shown that the extent of the upcoming movement can influence RTs and it is possible that the effects of extent on RTs differ for PD patients. To address this possibility a three-way ANOVA was carried out with Group (between factor), Precue (within factor) and Extent (within factor) as the experimental factors. Results indicated that RT did vary significantly as a function of movement extent ($F_{4,48} = 10.7$, $P < 0.0001$), greater extents being preceded by longer RTs as reported previously (Prablanc *et al.*, 1979; Pelisson *et al.*, 1986). This variation, however, was independent of the group (interaction: $F_{4,48} = 2.2$, $P > 0.07$) and precue (interaction: $F_{4,48} = 1.7$, $P > 0.09$) factors. As in the main analysis, a significant interaction between the group and precue type factors was observed ($F_{2,24} = 10.6$, $P < 0.0005$). The absence of interaction between movement extent and the precue factor is consistent with the fact that target distances were evenly balanced between the different precue conditions.

To summarize, the present results indicate that PD patients did not use the amplitude precue as efficiently as the direction precue. In other words, there was a specific cost of processing the amplitude precue in the PD group. The difference between the RTs in DP and AP conditions can be considered an indirect measure of this cost (Cost = $RT_{DP} - RT_{AP}$). Based on this measure, correlation analyses were performed to determine whether the impairment of the PD patients in using an amplitude precue increased with the severity of disease. General disease severity was estimated from the standard Hoehn and Yahr clinical scale whereas the specific severity of bradykinesia was estimated from the mean MD averaged across the three condition. Both correlation coefficients were positive. However, only the correlation between Cost and the severity of bradykinesia (MD) reached statistical significance (Cost vs. H & Y: $r = 0.61$, $P > 0.10$; Cost vs. MD: $r = 0.78$, $P < 0.04$).

Imaging data in normal subjects

Behavioural results were similar to those reported in the previous section for the control subjects. In brief, neither the parameters describing movement error (AE, DE: $F_{2,22} < 0.9$, $P > 0.35$) nor the movement duration ($F_{2,22} < 1.7$, $P > 0.20$) were affected by the precue factor. The only significant experimental effect was observed for RT ($F_{2,22} < 5.2$, $P < 0.03$). This parameter was reduced by the same amount irrespective of the nature of the precue provided prior to movement onset. As shown by *post hoc* analyses, RTs under the NP condition (363 ms) were significantly greater than under AP (351 ms) and DP (346 ms) conditions ($P < 0.05$). These two latter conditions were not different from each other ($P > 0.30$). Compared with data from the behavioural study, chronometric results from the imaging study showed a consistently smaller effect of precue on RT (i.e. smaller

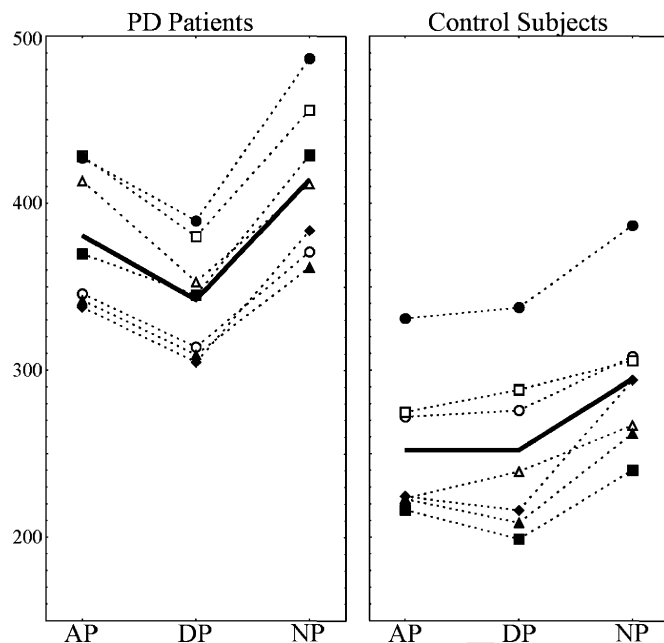


FIG. 3. Mean reaction time (RT) for each subject (thin lines) and the whole population (thick lines) as a function of the experimental conditions for the PD patients (left panel) and the control subjects (right panel).

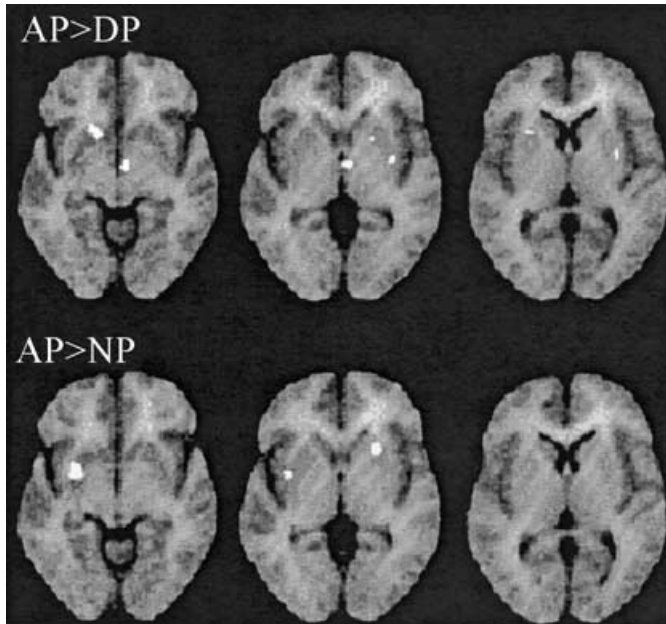


FIG. 4. Activation of basal ganglia during amplitude precue (AP) relative to the direction (DP, first row) and null cue (NP, second row) conditions. Areas in white are significant to $P < 0.01$. In the AP > DP comparison (upper row), activity is present in left caudal putamen (Talairach coordinates of the centroid: $-36, -5, 8$ mm), right rostral putamen ($16, 9, -6$) and left anterior thalamus ($-5, -12, -1$). In the AP > NP comparison (second row) there is activity in the left rostral putamen ($-24, 12, 3$) and right caudal putamen ($28, -3, -6$). The figure columns correspond to Talairach z-axis of $-9, -3$ and 3 mm relative to the anterior–posterior commissure axis. Image right is the left brain.

[Q30]

RT reductions). The difference may be explained by several factors that varied between experiments and that are known to influence motor RT. In particular, arm inertia differs depending on whether one is seated or lying down, muscle rigidity (cocontraction) is higher for vertical as opposed to horizontal movements, stress is a much more dominant psychological factor during PET scanning, and age might be a non-negligible source of variation (subjects were younger in the second study). Despite these differences, the behavioural results from both parts of the study indicated that normal subjects used AP and DP precues equally to speed movement preparation.

Imaging results revealed increased neural activity in rostral and caudal portions of the bilateral putamen for the AP conditions, where an amplitude precue was provided, relative to the DP and NP conditions. The location of the putamen activity is shown in Fig. 4. Differential activation of the left rostral putamen and right caudal putamen reached statistical significance for the AP vs. NP conditions, whereas activation was significant in the right rostral putamen, left caudal putamen and anterior thalamus in the AP vs. DP contrast. No activation was observed in the BG in the direction precue (DP) vs. amplitude (AP) or null cue (NP) comparisons.

At each of the five sites identified as significant by comparisons of AP vs. DP or NP conditions, rCBF was consistently maximal under the AP conditions (Fig. 5). What might appear to be dissimilar BG activations for the AP vs. DP and AP vs. NP comparisons (Fig. 4) can be explained by the differing effects of the DP condition at the different sites (Fig. 5). At three sites (right rostral putamen, left caudal putamen and left thalamus) the rCBF was suppressed under the DP condition below what was observed for the null (NP) condition. At the other two BG sites, rCBF under the DP condition was increased above that for the null condition.

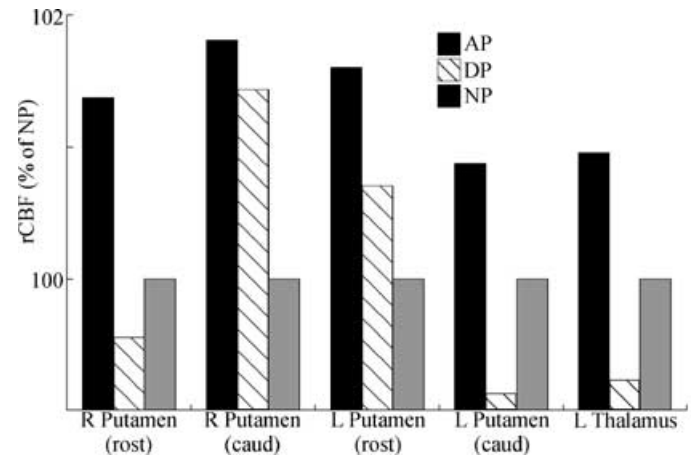


FIG. 5. Mean rCBF (normalized to the NP condition) at the five sites of maximal activation (see Fig. 4). For all sites, rCBF was maximal under the amplitude precue (AP) condition. Two of the sites (right caudal putamen and left rostral putamen), identified by the amplitude vs. null cueing contrasts, were activated to a lesser, nonsignificant degree by the directional precue (DP) condition. For the other three sites (right rostral putamen, left caudal putamen and left thalamus), rCBF was suppressed under the DP condition below what was observed for the null precue (NP).

Discussion

There are three main findings in this study. First, PD patients initiate a pointing response with shorter latencies when advance information about the characteristics of the forthcoming movement is available. Second, PD patients are distinctively impaired at using extent information to prepare the forthcoming movement. Third, a behavioural task requiring increased planning of movement amplitude produces increased activation in the BG network. These results are briefly discussed below. A potential mechanism through which the BG may selectively influence extent planning is proposed in the last section of the discussion.

PD patients are able to use advance information to prepare the forthcoming response

There has been a long controversy about the ability of PD patients to use advance information to plan upcoming movement. In most studies, simple RTs (SRTs) were compared in a patient population and a control group (Heilman *et al.*, 1975; Heilman *et al.*, 1976; Yokochi *et al.*, 1985; Bloxham *et al.*, 1987). In this case, the movement to be performed is known in advance, making it possible for the subject to preprogram a response. Results indicated that PD patients had significantly longer SRTs than control subjects. This observation was initially presented as reflective of an inability of patients to preprogram their response (i.e. to use advance information to plan the movement). This explanation, however, was challenged by potential alternatives such as increased muscle rigidity in PD patients. This controversy was addressed by comparing SRTs and choice RTs (CRTs). This second condition is identical to the former one except that the subject does not know in advance the characteristics of the upcoming movement. Consequently, the existence of a temporal deficit for SRT but not for CRT would support the idea that PD patients are impaired at using advance information. This prediction was corroborated in several studies (Bloxham *et al.*, 1984; Evarts *et al.*, 1981; Sheridan *et al.*, 1987; Pullman *et al.*, 1990) but not in others (Girotti *et al.*, 1986; Stelmach *et al.*, 1986; Lichter *et al.*, 1988; Pullman *et al.*, 1988; Jahanshahi *et al.*, 1992), thus leaving the issue unresolved.

A point of interest is that most previous studies involved very simple manual responses such as depressing a key with a finger or moving a lever (Bloxxham *et al.*, 1984; Everts *et al.*, 1981; Sheridan *et al.*, 1987; Lichter *et al.*, 1988; Jahanshahi *et al.*, 1992). These simple tasks may not be challenging enough to cause obvious variations in RT measurements in patients, leading to inconsistent results. In agreement with this view, studies that used complex tasks requiring the generation of goal-directed movements are the ones to show that PD patients are able to use advance information about the characteristics of the upcoming movement (Girotti *et al.*, 1986; Stelmach *et al.*, 1986; Weiss *et al.*, 1999). The results of the present study confirm and extend this observation. Indeed, our task can be considered complex for two reasons: (i) it required the generation of a structured goal directed movement; (ii) it presented the precue as a continuous range (line or arc of circle) and not as a very limited subset of discrete buttons or targets, as was often the case in previous studies (Girotti *et al.*, 1986; Stelmach *et al.*, 1986).

PD patients are selectively impaired at using advance information about movement amplitude

Several competing hypotheses have been proposed to account for the effects on movement RT of advance information about the characteristics of the upcoming response. It is therefore important to determine which among those hypotheses are compatible with our results and more generally with the selective impairment exhibited by the PD patients in using advance information about movement amplitude.

A first idea is that the initial precue acts by decreasing the number of response choices, thus allowing advance preparation of a limited number of motor plans (Goodman & Kelso, 1980). Hierarchical models of motor control suggest that this decrease might be different for direction and amplitude precues. To make this latter point clear consider, for instance, the model proposed by Schmidt and colleagues (Schmidt, 1975; Quinn & Scherwood, 1983). According to these authors, the first step of motor planning is to build a motor program to produce a given spatial pattern or to move in a particular direction. This program specifies both the phasing of the movement (temporal relationship of muscle contractions) and the relative forces (relationship of force magnitudes). In a second step the program is parameterized to the desired movement extent and velocity by specifying the 'gain' of the force magnitude. Within the framework of this model, and more generally of all similar hierarchical models, the DP condition allows specification of a unique program that has to be parameterized at target presentation (i.e. all targets can be acquired with a single program). By contrast, the AP condition imposes the specification of several programs, one of which has to be chosen at target presentation (all potential targets are no longer aligned so that they can be acquired with a single program). Based on these premises, one may propose that the deficit exhibited by the PD patients for the amplitude precue condition does not reflect a difficulty in parameterizing movement gain but rather an impaired ability to deal with multiple response choice tasks with respect to simple response choice tasks. Although this possibility cannot be formally rejected on the basis of our data, three main arguments suggest that it represents an unlikely explanation. First, our data from controls do not support the choice hypothesis. Indeed, in healthy subjects, multiple choice RTs have been shown repeatedly to be longer than simple choice RT (Hick, 1952; Girotti *et al.*, 1986; Stelmach *et al.*, 1986; Mahurin & Pirozzolo, 1993). Consequently, a longer RT should have been observed in AP than in DP if the number of choices was higher in the former condition. Our data contradict this prediction by showing similar RTs for these two conditions. Further arguments supporting this result can be found in behavioural studies showing, in healthy subjects, that the potential

number of response choices is unable to account for the RT-reducing effect of advance information (Bock & Arnold, 1992; Favilla, 1996; Bock & Eversheim, 2000). Second, chronometric observations do not support the idea that the number of potential choices would influence the RTs of PD patients differentially. Under the choice hypothesis, lengthened RTs for the AP condition would imply that parkinsonism has a more deleterious effect on choice than on simple reaction time tasks (i.e. a more deleterious effect in AP than in DP). Experimental observations do not support this claim, especially in the context of reaching movements (Girotti *et al.*, 1986; Stelmach *et al.*, 1986; Pullman *et al.*, 1988; for a review Gauntlett-Gilbert & Brown, 1998). Third, our data are not consistent in general with the hierarchical models underlying the choice hypothesis. No difference in RTs was observed between AP and DP experimental conditions for normal subjects in the present study, while a larger decrease should have been observed for DP according to hierarchical models. Indeed, a direction precue should allow the RT to decrease significantly by allowing a preplanning of a motor program prior to movement onset. By contrast, an amplitude precue should be useless if the motor program to be scaled is not defined. Further arguments supporting these claims can be found in behavioural results showing that the influences of amplitude and direction precues on RT are independent and additive (Rosenbaum, 1980; Lepine *et al.*, 1989).

A second candidate idea to account for the pattern of precue effects observed here is that precues produce a nonspecific increase of 'attention' in the motor system. In agreement with this idea, it was shown that precues that provide a subject with unusable information can allow some reduction in RT. Also, it was found that precues reduce RT even when the subject has to react to the actual target presentation by a simple predetermined tapping movement (Bock & Eversheim, 2000). Theoretically, the 'attentional hypothesis' predicts that the RT reduction depends only on the size of the precued spatial area. This prediction does not agree with the observation that the same pair of stimuli (extent or direction precues) resulted in similar RT reductions in one group (controls) and different reductions in another (PD). The inability of the attentional hypothesis to explain the larger effect of the precue factor in DP with respect to AP is also reinforced by the fact that the precued area (i.e. the length of the precue line) was, on average, comparable in the DP (212 mm) and AP (225 mm) conditions. Thus, the attentional hypothesis alone cannot account for the precue effect observed in the present study.

A third potential explanation for our results is that movement planning is a parallel-parametric process involving independent specification of the movement amplitude and the movement direction (Rosenbaum, 1980; Bock & Arnold, 1992; Ghez *et al.*, 1997). As emphasized in the introduction, this hypothesis is substantiated by numerous observations gathered in various domains. Under this hypothesis, PD patients show a smaller RT reduction in AP than in DP because they are selectively impaired at planning movement amplitude. This conclusion agrees with a recent behavioural study showing preserved control of movement direction together with impaired control of movement amplitude in PD patients with respect to control subjects, when the movement is performed without vision of the moving limb and when the confounding effect of systematic errors in the estimation of the initial hand location is offset (Desmurget *et al.*, 2003). In that study, the specific pattern of extent errors exhibited by the PD patients was shown to be incompatible with a feedback-related deficit. It is worth mentioning that a specific difficulty of the PD patients in planning movement amplitude could be one of the factors that causes these patients to exhibit longer RTs than controls in various motor tasks (Heilman *et al.*, 1975; Heilman *et al.*, 1976; Yokochi *et al.*, 1985; Bloxxham *et al.*, 1987).

The BG contribute to the planning of movement extent

The results of the behavioural study in PD are consistent with the idea that these patients have specific difficulties planning movement extent. This finding by itself, however, leaves ambiguity about the anatomical source(s) of the deficit and thus whether the intact BG are really involved in planning movement extent. Although PD is associated with a relatively circumscribed dopaminergic denervation of the BG 'motor circuit' (Wichmann & DeLong, 1996; but see Braak & Braak, 2000), functional abnormalities have been observed not only in the BG and in the frontal cortical areas that are primary recipients of BG outflow (Playford *et al.*, 1992; Jahanshahi *et al.*, 1995), but also in other structures including the brainstem, the parietal cortex and the cerebellum (Catalan *et al.*, 1999; Rascol *et al.*, 1997). As a consequence, impaired use of the extent precue in PD could reflect a dysfunction of other CNS networks independent of or secondary to the abnormal BG outflow known to be associated with PD. With respect to this point, it is in particular well established that the primary pathology of PD gives rise to chains of functional changes in the cerebellum and the primary sensory-motor cortex, i.e. in two structures that may be important nodes in the network that controls movement scale (Turner *et al.*, 1998, 2003). These reservations, however, do not apply to our functional imaging experiment, in which we tested directly whether the BG network is differentially involved in amplitude planning. We found that a behavioural condition that emphasized movement extent planning (condition AP) resulted in enhanced activation of BG structures in comparison with task conditions that emphasized movement direction planning (DP) or no planning (NP). This finding is consistent with the idea that neuronal activity in the BG contributes directly to the control of movement extent. Such a conclusion suggests that the impaired amplitude planning observed in PD patients, in the first experiment, was (at least partially) due to a dysfunction of the BG network.

To avoid ambiguity, it is worth mentioning that these results should not be taken to mean that movement extent is under the sole influence of the BG network. Electrophysiological studies suggest that the BG may act in conjunction with a network of cortical and cerebellar areas. In particular, single-unit recording studies in nonhuman primates have identified neurons in cortical, cerebellar and BG motor areas with patterns of activity that reflect the planning or control of movement extent (Georgopoulos *et al.*, 1983; Fu *et al.*, 1993; Riehle *et al.*, 1994; Fu *et al.*, 1995; Turner & Anderson, 1997; Messier & Kalaska, 2000). Nearly always, however, the activity of the same neurons also encoded other parameters of movement such as movement direction (Messier & Kalaska, 2000), required precision and arm geometry (Scott & Kalaska, 1997; Scott *et al.*, 1997). Recording studies in cortex and cerebellum have typically found amplitude or velocity effects in a minority of the cells examined (Riehle & Requin, 1989; Taira *et al.*, 1996; Fu *et al.*, 1997; Coltz *et al.*, 1999; Messier & Kalaska, 2000), whereas two studies in BG structures reported amplitude and/or velocity effects in a majority of the neurons sampled (Georgopoulos *et al.*, 1983; Turner & Anderson, 1997). Although those studies restricted their sampling to the posterior BG 'motor' circuit, their results are consistent with the conclusion of the present study, namely that extent-related information is encoded in BG structures. When considered together with electrophysiological studies, the present results are consistent with our initial hypothesis that movement amplitude results from the combined activity of several cortical, subcortical (BG) and cerebellar areas. As emphasized by Vindras & Viviani (2002), the failure of modelling studies to identify a satisfying algorithm to derive movement amplitude from electrophysiological activity in cortical and subcortical structures support this conclusion

(such an algorithm exists for movement direction; Georgopoulos, [Q16] 1995).

The BG is organized as a series of distinct parallel pathways each of which is associated with a different frontal lobe function (Alexander *et al.*, 1990). The posterior-lateral basal ganglia participate in low-level motor control functions, whereas more anterior-medial BG regions contribute to associative and limbic functions (Middleton & Strick, 2000). The results of the present study agree with this dissociation. For the experimental condition requiring amplitude planning (AP), the primary loci of activation in the basal ganglia were in posterior and middle portions of the putamen bilaterally (Fig. 4). A similar pattern of bilateral basal ganglia activation has been observed in recent imaging studies of brain activity correlated with the extent and velocity of arm movement (Turner *et al.*, 2003) and with alterations in the 'gain' for movement extent and velocity (Krakauer *et al.*, 2004). These regions of the striatum receive strong bilateral input from motor and premotor cortices (Flaherty & Graybiel, 1991; Takada *et al.*, 1998) and are considered part of the basal ganglia skeletomotor circuit (Alexander *et al.*, 1990). As such, they can influence movement planning in the motor and premotor cortices by way of projections through globus pallidus and thalamus (Hoover & Strick, 1993). The bilateral nature of the activations observed in the present study is consistent with the observation that the learning of a novel gain factor during adaptation experiments generalizes between limbs (Bock & Arnold, 1992; Vindras & Viviani, 2002). At the same time, however, it is in partial contradiction with several motor imaging studies in which contralateral putamen activations were reported. At a first level, this difference might be related to technical and statistical issues. In particular, the hypothesis-driven approach used in the present experiment favoured statistical sensitivity by focusing on the BG network (at the expense of comprehensiveness, however; see Materials and methods). At a second level, it might be that the pattern of activation in the BG network is dependent on the type of task being performed. In a study that manipulated the distance and precision requirements of a reciprocal reaching task, Winstein and colleagues (Winstein *et al.*, 1997) found that greater targeting precision (as opposed to greater limb transport) activated the anterior ventral striatum (caudate). More recently, Siebner *et al.* (2001) reported increased activation of anterior dorsal putamen during handwriting performed under slow feedback (as opposed to fast open-loop) conditions. In a study that manipulated the velocity and rate of reversal of smooth pursuit tracking, increasing movement velocities led to a concordant monotonic increase in the activation of left posterior globus pallidus, part of the BG 'motor circuit' (Turner *et al.*, 1998). In all of these studies, manipulations of the amplitude or velocity of movement led to differential activation of BG structures. This sensitivity to the nature of the task might suggest that different putamen activations were observed here in the AP > DP and AP > NP subtractions due to the existence of different sensorimotor processing in NP and DP conditions. In agreement with this view, Fig. 5 shows that the DP condition has different effects at different sites in the BG network when compared to the NP condition (even if rCBF increases were largest under the AP condition at all sites). For the right rostral putamen, the left caudal putamen and the left thalamus the rCBF was suppressed under the DP condition below what was observed for the (null) NP condition. By contrast, for the right caudal putamen and the left rostral putamen, rCBF under the DP condition was increased above that for the (null) NP condition. [Q17] [Q18]

In summary, the present results are clearly supportive of a role for the BG in advance planning of movement extent. Beyond this point, however, it should be mentioned that our data do not rule out the possibility that the BG also contribute to the feedback control mechanisms described in the introduction. In addition, our data are not

incompatible with the fact that nonmotor BG circuits may contribute to cognitive and limbic functions not explored by this study (Middleton & Strick, 2000).

BG modulate cortical activity and/or the tuning of the spinal interneuronal circuits

Beyond the present findings, it remains to be understood how the BG contribute to the planning of movement amplitude. Although the answer to this question is not known, two plausible hypotheses can be tendered. The first hypothesis, recently endorsed by Berardelli *et al.* (2001), proposes that BG output reinforces the cortical mechanisms that prepare the commands to move. Compelling support for this model can be found in neurophysiological data suggesting that: (i) motor and premotor cortical areas are involved in the planning of movement amplitude (Fu *et al.*, 1993, 1995; Kurata, 1993; Riehle *et al.*, 1994; Messier & Kalaska, 2000); and (ii) the activity of these areas is significantly disordered in PD patients during the performance of various motor tasks (for a review see Berardelli *et al.*, 2001). A second hypothesis, not necessarily incompatible with this central view, is the idea that movement extent depends on the appropriate tuning of spinal circuits, such as presynaptic inhibition of the Ia monosynaptic reflex in the antagonist muscles prior to movement onset. Two findings seem especially relevant with respect to the present discussion. First, in contrast with healthy subjects, PD patients show little or no decrease of Ia reciprocal inhibition at the onset of fast wrist movements (Meunier *et al.*, 2000). Second, presynaptic inhibition of monosynaptic Ia terminals is reduced in PD patients (Morita *et al.*, 2000). Theoretically, the abnormalities just described are likely to affect movement amplitude (even if it is not evident at this point why an alteration in reciprocal inhibition would affect movement extent only). Impaired peri-movement modulation of reciprocal Ia inhibition will undermine the descending motor command to agonist motoneuron pools by: (i) insufficient presynaptic inhibition of antagonist monosynaptic Ia terminals, and (ii) through an increased inhibition of the reciprocal Ia inhibitory interneurons projecting onto antagonist motoneurons. This combined action could result in a decrease of movement amplitude. It is worth noting, however, that although available evidence does indicate that antagonist EMG activity during movement may be increased in PD subjects (Pfann *et al.*, 2001), the increase is minor, not always observed, and thought unlikely to account, by itself, for the dramatic slowing and hypometria observed in PD (Johnson *et al.*, 1991; Pfann *et al.*, 2001).

Conclusion

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 may explain the often-reported tendency of PD patients to exhibit hypometria when required to point to visual targets without vision of the limb. Although the exact mechanism by which the BG contribute to the planning of movement extent has yet to be elucidated, we suggest that this structure participates in extent planning by modulating cortical activity and/or the tuning of the spinal interneuronal circuits.

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Abbreviations

AE, amplitude error; AP, amplitude precue; BG, basal ganglia; CRTs, choice RTs; DE, direction error; DP, direction precue; MD, movement duration; NP, no

precue; PD, Parkinson's disease; PET, positron emission tomography; rCBF, regional cerebral blood flow; RT, reaction time; SRTs, simple RTs.

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[Q28]

[Q29]

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28	Wichmann & DeLong 1998 not in the text!	
29	Woods 1998 : <u>two references, so labelled a and b.</u> Please check that all text citations are correct.	
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