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Deficits in Rapid Adjustments of Movements According to Task Constraints in Parkinson's Disease

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Abstract: The role of the basal ganglia in the adaptive control of movement was investigated by unexpectedly perturbing movements in 8 patients with Parkinson's disease (PD) tested off medication and in 6 aged-matched healthy subjects. Subjects performed two movement components simultaneously and without visual feedback: touching the nose with the finger while leaning the trunk forward. Subjects wore a harness connected to an electromagnet, which was attached to a wall. The trunk movement was mechanically blocked in randomly selected trials by engaging the electromagnet. While healthy subjects performed the task equally well in both conditions, PD subjects' hand movements significantly deteriorated in trunk-perturbed compared to trunk-free trials. Deteriorated hand movements were characterized by segmented hand paths, unsmooth velocity profiles, and prolonged movement times. This finding indicated that the relatively local trunk perturbation had a global effect on the hand movement of PD subjects, necessitating them to reinitiate, after some delay, their arm movement in perturbed trials. Thus, the basal ganglia may be a critical node in brain networks mediating the flexibility of responses to altered motor states. © 2004 Movement Disorder Society

Key words: response to perturbation; multisegmental control; basal ganglia; trajectory formation; frames of reference

The ability to switch rapidly between different coordinations depending on changes in the environment is a fundamental characteristic of everyday motor activity.[1] This ability largely depends on accurate and efficient integration of sensorimotor processes in a context-dependent way. While basic motor components are likely generated by spinal centers, the organization of different components into a complex behaviour is likely produced by supraspinal and cortical centers.[2,3] The basal ganglia (BG) may be critical for the flexible use of multiple movement repertoires given the BG's extensive reciprocal connectivity with cortical and subcortical neural centers[4] and their known involvement in sensorimotor integration processes.[5–8]

Despite the breadth of studies implicating the BG in motor execution and higher-level sensorimotor integration,[9] our understanding of their involvement in adaptive control—allowing individuals to reach the motor goal, despite changing environments—remains limited. Analyses of the behaviour of patients with Parkinson's disease (PD) may provide a unique window into the function of the BG. PD is very well characterized clinically, neurochemically, and neurophysiologically, allowing strong corollaries to be drawn between experimental and clinical observations.

The role of the BG in adaptive behaviour has been commonly studied in PD patients by displacing a visual target and analyzing the subject's response to the perturbation.[10] Visual perturbations, however, may not capture key elements of adaptive control because of PD patients' known reliance on visual cues[11] that often improve their performance.[12] Given the motor

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deficits of PD patients, it is critical, therefore, to analyze adaptive behaviour by using motor perturbations. In this respect, postural perturbation paradigms might be appropriate,[13,14] but they introduce other variables (e.g., fear of falling) that may alter the adaptive response.[15] With respect to the generalization of these findings to upper limb control, the results of such studies are not conclusive, which is consistent with observations that levodopa differentially affects upper and lower limb control.[16] The nature of rapid responses of the upper limb to motor perturbations remains virtually unexplored in PD patients.

In the present study, we examined the ability of PD patients in the off medication state to adapt upper limb control to motor perturbations of the trunk. PD patients and aged-matched healthy subjects, after short-duration training, touched the nose with the finger (a test used in standard neurological examinations) while simultaneously leaning the trunk forward. The trunk movement was mechanically prevented in randomly selected trials. While subjects were instructed to perform the hand and trunk movements simultaneously, we compared the hand kinematics in two types of trials, when the trunk movement was unrestrained or unexpectedly blocked. In other words, the experimental paradigm required subjects to rapidly switch from one type of coordination to another, depending on whether the trunk motion was restricted or not.

We hypothesized that healthy subjects would have no difficulty in preserving their arm coordination pattern, despite unexpected perturbations of the trunk. In contrast, if the basal ganglia are critical nodes in a network mediating flexible and adaptive responses to altered motor states, then the unexpected trunk perturbation should have a destabilizing effect on the finger–nose component of the movement in PD subjects.

SUBJECTS AND METHODS

Subjects

Six healthy subjects and 8 nondepressed and nondemented patients (assessed with the Beck Depression Inventory and the Mini-Mental Examination, respectively) with idiopathic PD (see Table 1) participated after signing consent forms approved by Rutgers University and the Rehabilitation Institute of Montreal. PD patients were tested in the morning before taking their first dose of antiparkinsonian medication of the day, being off medications for at least 12 hours after their dose of the previous night, ameliorating the majority of the beneficial effects of dopamine replacement therapy.[17]

Procedure

A schematic of the setup and task is illustrated in Figure 1A. Subjects learned a two-component task as described above. They were instructed to perform these components synchronously in response to an auditory go signal. Subjects wore a vest harnessing a metal plate on the back, which between trials was locked to an electromagnet (Warner Electric, Inc.) attached to a wall. On 60% of randomly selected trials, unrestrained trunk motion was allowed by deactivating the electromagnet at the time of the auditory signal (Free condition). On the remaining 40% of the trials, trunk motion was blocked (Blocked condition) by keeping the electromagnet activated during the trial. Subjects wore liquid crystal glasses (Translucent Technologies, Inc.) that became opaque upon an electric signal that was synchronized with the go signal. Subjects were warned before the beginning of the experiment that such Blocked trials may occur, but were instructed to command trunk movement and touch the nose with the finger as if nothing happened.

TABLE 1. *Clinical characteristics of Parkinson's disease subjects*

Patient	Sex	Age (yr)	Duration of illness (yr)	UPDRS Motor score	PD stage (18)	Medication
PD 1	M	50	5	23.5	II	LR, P
PD 2	F	66	7	31	II	A, LR, P
PD 3	M	71	6	26	II	A, LR, Ph, Pm
PD 4	F	49	7	27	III	B, LR, R
PD 5	M	64	17	24	III	LR, Pm, S
PD 6	M	72	11	47	III	LR, P
PD 7	F	73	8	21	II	LR
PD 8	M	64	17	24	II	LR, Pm, S
PD mean ± SD		64 ± 9	9.8 ± 4.8	27.9 ± 8.2		
Control mean ± SD		69 ± 14				

Clinical status and medications for Parkinsonian subjects; *A,* amantidine; *B,* baclofen; *LR,* sustained release L-dopa with carbidopa; *P,* pramipexole; *Ph,* paroxetine hydrochloride; *Pm,* pergolide mesylate; *S,* selegiline; *R,* ropinirole. UPDRS, Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease.

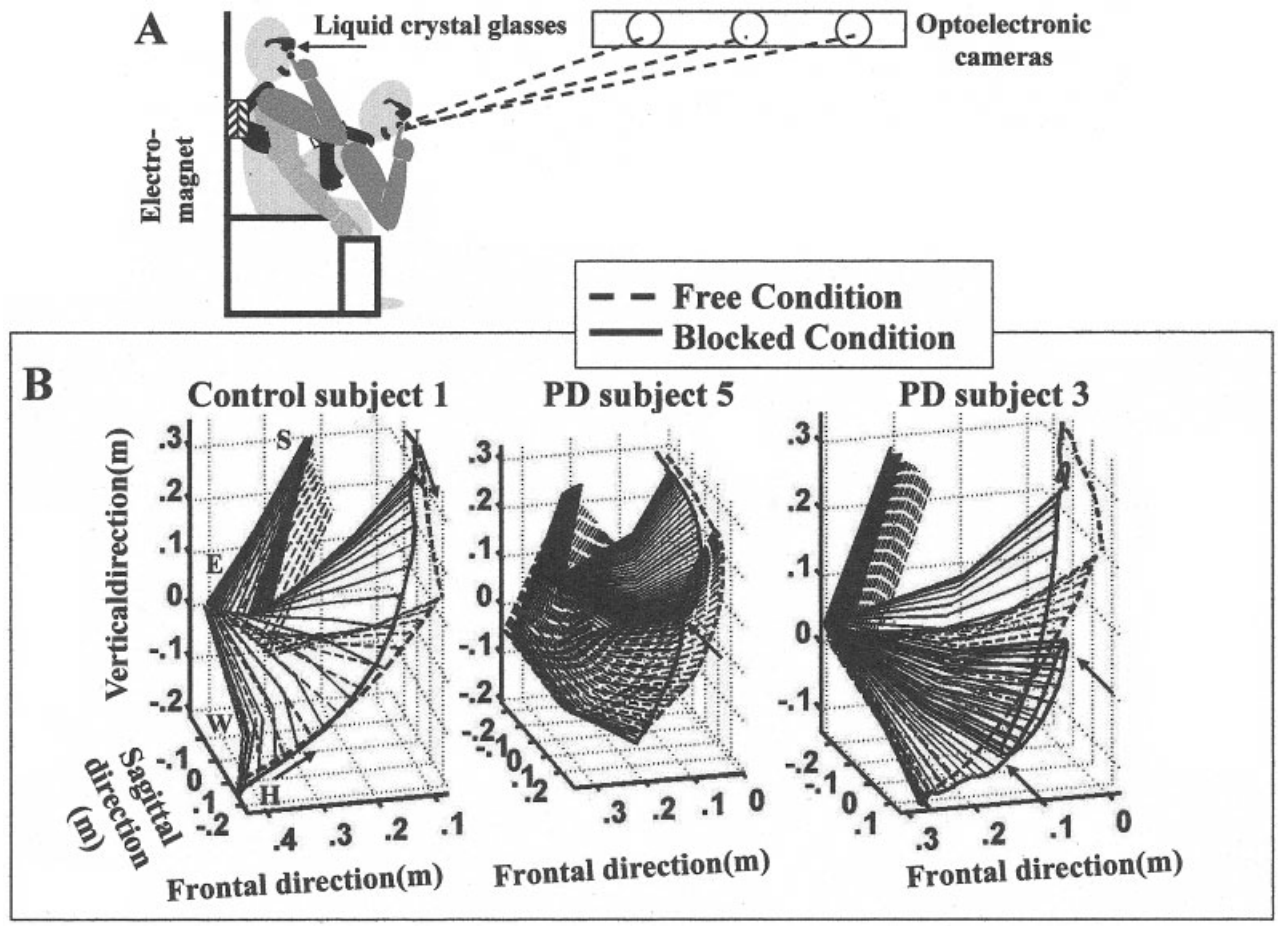

FIG. 1. A: Trunk perturbation paradigm. **B:** Three-dimensional strobe plot of the finger, wrist, elbow, shoulder, and nose trajectories for 1 control (left) and 2 Parkinson's disease (PD) subjects. One nonperturbed (hatched) and perturbed (solid) trial is shown for each subject. Each strobe is plotted every 30 msec. Arrows demarcate points of movement irregularities in the Blocked condition. The middle panel represents the movement slowing that was noted in 7 of 8 PD subjects, and the right panel shows the remaining PD subject whose hand movement stopped after the trunk perturbation, reversed direction, and then restarted back to the nose. N, nose; S, shoulder; E, elbow; W, wrist; H, hand.

Data Acquisition

Arm–trunk kinematics were derived from position data of seven infrared emitting diodes (IRED) attached to the following locations: between the lenses of the glasses, the bony landmarks of the lower sternum, acromion processes of both scapulae, lateral epicondyle of the elbow, wrist styloid, and index fingertip. Each IRED's position was captured by optoelectronic cameras (Optotrak 3010, Northern Digital, sampling rate 100 Hz). Offline, missing samples were interpolated (a five-point algorithm) and the data were low-pass filtered at 8 Hz.

Kinematic Variables

By using customized software,[19,20] movement onset was defined as the time at which the tangential hand velocity first exceeded 5% of the peak velocity (measured in an absolute frame of reference), and movement offset, the time when finger-to-nose contact occurred. Onset times of the hand, nose, and trunk were compared for onset synchrony. Hand movement time (MT) was analyzed as the time interval between the onset and offset. The onset of the perturbation was defined as the time at which the mean trunk tangential velocity in the Free condition exceeded and remained outside the mean + 1 standard deviation (SD) of the Blocked condition. These variables were also calculated for hand kinematics analyzed in a head-centered frame of reference. Hand coordinates in this frame of reference (which we will sometimes refer to as "body space"), $X'_{hand}(i)$, $Y'_{hand}(i)$, and $Z'_{hand}(i)$, were calculated for each sample by subtracting the coordinates of the nose's tip from those of the index fingertip.

Hand Paths.

To quantify hand paths in body space, points along the path spaced every 10% of the total trajectory length were demarcated and connected by a line. The angle between each pair of adjoining lines was computed to yield nine deviation angles per trial. The absolute difference between each Blocked condition's deviation angle and the mean of the respective angle of the Free condition was calculated as the divergence angle. The mean of the nine angles was the mean divergence angle.

Velocity Profiles.

Position data in external and body space were differentiated to compute velocity profiles in external and body space, respectively. Between-condition invariance was quantified in body space by analyzing the peak velocities and the times at which 25, 50, 75, and 100% of the peak velocities were reached (phase shift) during the accelerating phase of the movement.

Jerk.

Normalized integrated jerk (NIJ) score was computed as an indicator of hand movement smoothness:

$$\mathrm{NIJ} = \mathrm{sqrt}[(T^5/2L^2)\int J^2 dt],$$

where J is the third time derivative of hand position in body space, sqrt is square root, T is movement duration, L is hand path length, and the limits of integration are (0,T). This measure is relatively independent of movement duration and amplitude.[21–23]

Movement Tardiness Index.

Mostly in PD subjects, the trunk arrest influenced the hand movement by slowing it, and on rare occasions even completely stopping it. In the latter case, the hand movement was reinitiated after some period of time. In the former case, the hand velocity, although decreased, remained above zero and could fluctuate about an almost constant level for a given period of time. Each period greater than 50 msec during which these fluctuations did not exceed 3% of the hand peak velocity (measured in the external, laboratory, frame of reference) was considered as a velocity plateau and the total duration of these plateaus in each individual trial of each subject was computed to characterize the movement tardiness effect of the trunk perturbation. We call this duration the movement tardiness index.

Statistics

Variables were subjected to a repeated measures analysis of variance (ANOVA) with one between-factor Group (Control, PD) and one within-factor Condition (Free, Blocked). A Student–Newman–Keuls test was used for post hoc analysis. Effects on a given measure were considered to be significant if $P < 0.05$. A PD subject's peak velocity and velocity phase were deemed significantly different if their value exceeded the mean + 2 SD (95% confidence interval) of the healthy subjects. NIJ score was analyzed with nonparametric statistics (Mann–Whitney for unpaired data and Wilcoxon signed rank test for paired data) because of distribution assumptions not being met by the PD group. Significant Group effects reflect general deficits related to PD, whereas significant Group × Condition interactions reflect a perturbation-related deficit.

RESULTS

The onset of nose, trunk, and hand movement did not differ between the two groups ($F(1,12) = 0.1$, $P = 0.7$). Furthermore, movement was initiated at the head, trunk, and hand synchronously in healthy subjects and PD patients (Group × Body segment interaction, $F(1,12) = 0.4$, $P = 0.7$), suggesting that neither healthy subjects nor PD patients segmented the movement at the onset, before the perturbation. The onset latency of the trunk perturbation did not differ across groups (group means, control, 42.2 ± 12.7 msec; PD, 65.3 ± 33.4 msec; $t = -1.6$, $P = 0.14$), indicating that the perturbation occurred at similar times in the movement for the two groups.

Figure 1B shows the finger and nose paths in external space for 1 healthy and 2 PD subjects. Figure 1B shows that, while hand movements remained similar between the healthy and PD subjects in the Free condition (hatched lines), PD subjects often exhibited spatiotemporal irregularities (see Movement Tardiness Index section in the Subjects and Methods section) in trunk-perturbed trials. The arrows along the black traces of the middle and right panels of Figure 1B demarcate periods of time in which the hand paths became segmented after the perturbation. Figure 2A (top) shows that the movement tardiness index was minimal in the control group (mean, <16 msec in either Condition) but was significantly longer in the PD group (63 ± 53 and 190 ± 137 msec in Free and Blocked conditions, respectively; Group main effect, $F(1,12) = 8.6$, $P = 0.01$) and Group × Condition interaction, $F(1,12) = 9.5$, $P < 0.01$). Post hoc testing showed that, while no significant differences between the Free and Blocked conditions were present in the control group, the movement tardiness index was significantly longer in the Blocked vs. Free condition in PD patients.

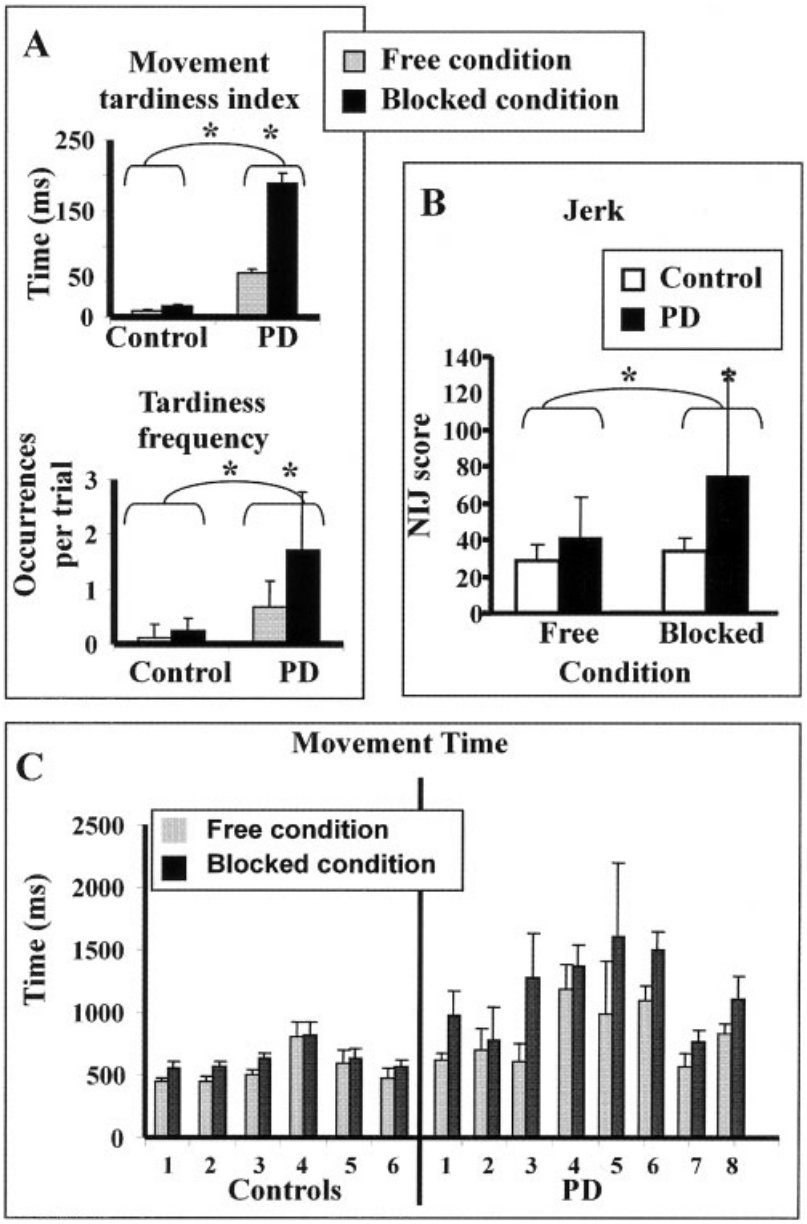

FIG. 2. A: Movement tardiness index and frequency of tardiness episodes per trial. **B:** Hand movement smoothness (normalized integrated jerk [NIJ] score). **C:** Movement times for each subject in nonperturbed and perturbed conditions. PD, Parkinson's disease.

Furthermore, as illustrated in Figure 1B, only one to two tardiness periods were evident during a given Blocked condition trial in the PD subjects (group mean, 1.7 ± 1, see Fig. 2A, bottom), indicating that this segmentation could not be attributed to other movement irregularities such as tremor. Tardiness periods were significantly less frequent in the PD subjects' Free condition (0.7 ± 0.5 per trial) and were very rare in the control group ($<0.3 \pm 0.2$ per trial). The stability of the hand was further analyzed using the NIJ score (see Subjects and Methods section). While NIJ scores of the Free condition did not differ significantly across groups ($U = 10$, $P = 0.07$), PD subjects' NIJ scores were significantly elevated in their Blocked relative to the Free condition ($P = 0.01$; Fig. 2B). Moreover, PD subjects' Blocked condition NIJ scores were significantly greater than those of the controls ($U = 8$, $P = 0.04$). This finding suggests that, while PD and control subjects' movements were comparably smooth in the Free condition, the markedly longer and more frequent hesitations noted in the PD subjects' Blocked condition led to significantly more irregular movements. This statistical pattern was the same when hand NIJ scores were analyzed in a frame of reference relative to the nose or relative to external space.

PD subjects' movements were bradykinetic relative to those of the controls. The peak tangential hand velocity in the Free and Blocked conditions, respectively, was 1 ± 0.37 and 1 ± 0.42 m/sec for the PD subjects and 1.8 ± 0.21 and 2 ± 0.32 m/sec for the controls. This Group effect was significant ($F(1,12) = 23.4$, $P < 0.001$). Of interest, the Group × Condition interaction was not significant ($F(1,12) = 3.8$, $P = 0.07$), indicating that peak velocity was not affected by the perturbation in the PD subjects.

Consequential to the bradykinetic movements of the PD subjects, Figure 2C shows that their MT was longer than that of controls in the Free and Blocked conditions, respectively (PD, 820 ± 239 and 1,171 ± 317 msec; Controls, 544 ± 138 and 628 ± 97 msec). The Group effect for MT was significant ($F(1,12) = 12.7$, $P < 0.004$). Additionally, a significant Group × Condition interaction for MT ($F(1,12) = 24.8$, $P < 0.001$) indicated that this difference interacted with the trunk perturbation condition. Post hoc analysis revealed that while control subjects' MT did not differ significantly between the Free and Blocked conditions, PD subjects' did. In other words, the PD subjects showed a significantly larger increase in MT relative to the control group in perturbed trials.

Because the target was defined as a point on the body, invariance of the hand trajectories between the Free and Blocked conditions was analyzed in body space. Figure 3 shows one control subject's hand paths (top) and velocities (bottom) when plotted in a frame of reference relative to the head. As a group, the control subjects' hand paths remained relatively invariant across conditions with the mean trajectory divergence not exceeding 3.6 ± 1 degrees. Likewise, the hand velocity profiles remained relatively invariant with regard to peak velocity (group mean, SD, −0.89 ± 0.35 and −0.98 ± 0.33 m/sec in the

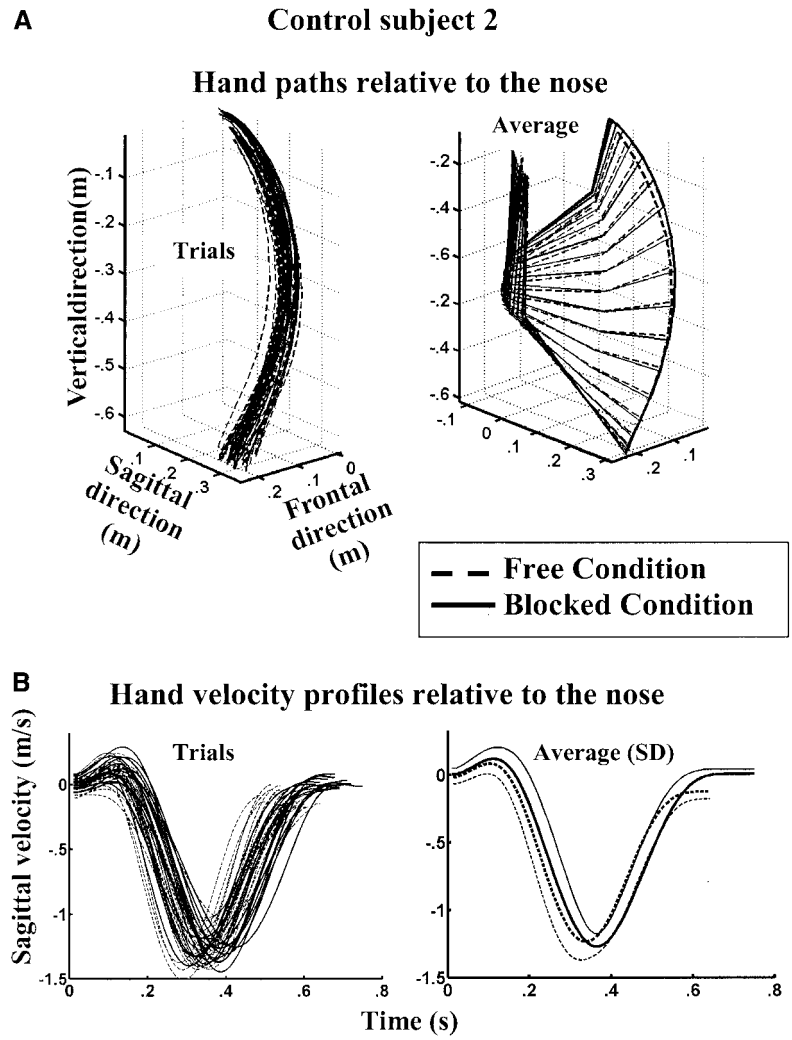

FIG. 3. A control subject's hand trajectories in a frame of reference relative to the head. Individual trials (left panels) and respective averages (right panels) are shown for the nonperturbed (hatched) and perturbed (solid) conditions. Extra pre- and postmovement samples have been plotted for clarity.

Free and Blocked conditions, respectively) and phase (mean overall phase shift for the Blocked condition, 26 ± 18 msec).

The degree of invariance between the hand paths of the Free and Blocked conditions was heterogeneous in the PD group. Figure 4A (left) shows 1 of 2 PD subjects (PD 5 and PD 3) for whom the mean divergence far exceeded the mean + 2 SD (95% confidence interval) of the control group (mean, 42.3 ± 5.4 degrees). Figure 4B (left) shows 1 PD subject representing the remaining 6 PD subjects for whom the mean trajectory divergence did not exceed that of the 95% confidence interval of the control group (mean, 4.1 ± 1.5 degrees). As a group, the PD subjects' trajectory divergence did not significantly differ from that of the Controls' ($F(1,12) = 1.9$, $P = 0.9$).

As stated above, the control subjects' velocity profile in the Blocked condition was delayed relative to the Free condition by a mean 26 ± 18 msec. In contrast, the delay was markedly longer in PD subjects (group range, 41.5–410.4 msec). Figure 4B (right) shows 1 of 4 PD subjects for whom the velocity profile in the Blocked condition was distinctly delayed relative to that of the Free condition. The delay in each of these 4 subjects exceeded the 95% confidence interval of the controls. Of interest, the difference between peak velocity values remained within the 95% confidence interval of the control group, indicating that this was actually a delay in the profile rather than a change in its shape. Figure 4A (right) shows 1 of 4 PD subjects for whom it was impossible to determine whether or not the velocity profile remained invariant regardless of conditions due to markedly increased variability. The marked delay in the hand velocity profile in the Blocked condition, not observed in the control group, indicates that the trunk perturbation substantially influenced on the hand trajectory.

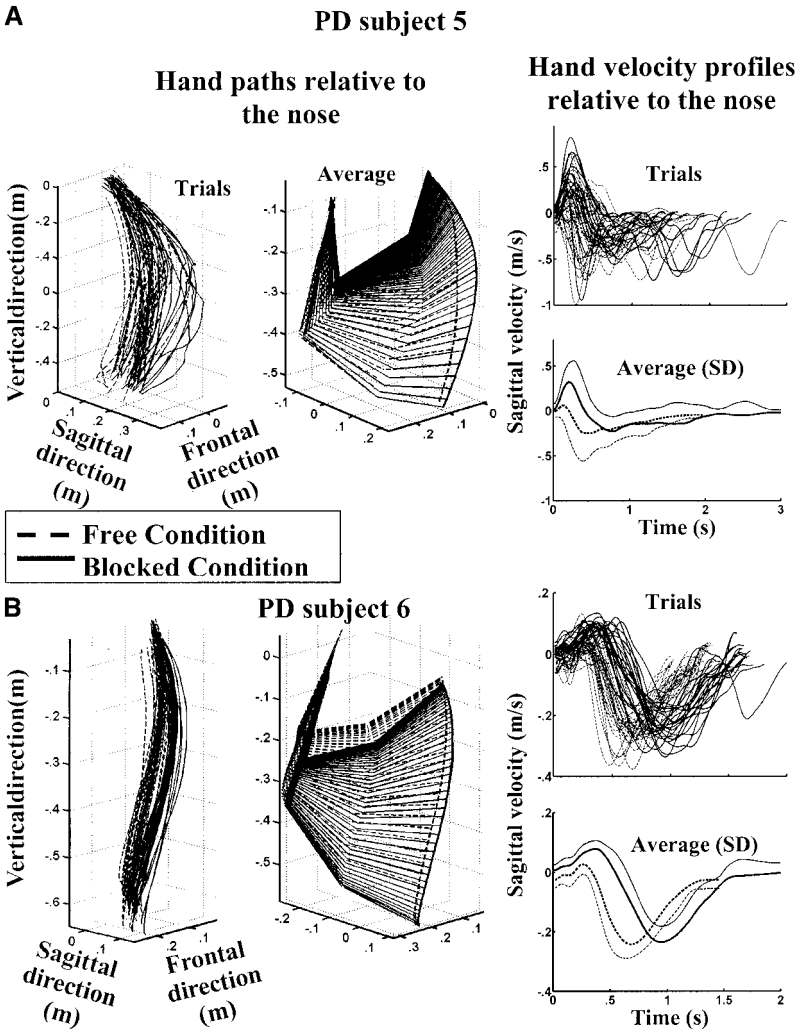

FIG. 4. The hand trajectories of 2 Parkinson's disease (PD) subjects relative to the head. Individual trials and respective averages are shown for the nonperturbed (hatched) and perturbed (solid) conditions. Extra pre- and postmovement samples have been plotted for clarity.

Contact made between the finger and nose served to inform subjects of the completion of the movement, providing knowledge of results. We, therefore, investigated whether any learning occurred across trials. To analyze learning effects, each subject's NIJ score was divided into six blocks per condition. A three-way ANOVA was performed with Group (PD, Control), Condition (Free, Blocked), and Trial block (1–6) as factors. The mean NIJ score in the perturbed condition remained constant across the six blocks for the control subjects (block 1 vs. 6, 33 ± 8 vs. 32 ± 8) and for PD subjects (77 ± 59 vs. 76 ± 71). Moreover, the variability did not improve in either group across blocks. This finding of a lack of learning was supported by a nonsignificant Trial Block main effect ($F(1,5) = 0.52$, $P = 0.76$) and nonsignificant second- and third-order interactions of Trial Block with Group and/or Condition.

We analyzed whether the context-dependent impairment in the PD group was correlated with the clinical manifestations of the disease. For this, bradykinesia of the right upper extremity (pointing arm) was calculated as the sum of the Unified Parkinson's Disease Rating Scale scores for finger taps, hand grips, and pronation/supination scores (maximum score = 12). Bradykinesia was correlated with the between-condition difference (Blocked–Free) of two dependent variables, MT and NIJ score. No significant correlation was noted between bradykinesia and either of the two variables (MT, $r = 0.2$, $P = 0.6$; NIJ score, $r = 0.03$, $P = 0.9$).

DISCUSSION

The primary focus of the present experiment was to investigate the ability of PD patients and aged-matched healthy subjects to preserve their arm coordination pattern when the trunk movement was unexpectedly blocked. Most substantial differences in responses between the two populations of subjects were revealed when the hand movements were represented in a frame of reference that moved together with the head. Measured in this frame, the healthy subjects' hand trajectory and its smoothness remained invariant across the Free and Blocked conditions, leading to preserved movement time. This finding suggests that healthy subject were able to reproduce the same control pattern for arm muscles whether the trunk motion was blocked or not. In contrast, in response to the trunk perturbation, PD subjects delayed the finger-to-nose movement, as evident from the delay in the hand velocity profile in the Blocked-trunk condition. In other words, unlike control subjects, PD subjects were unable to prevent the influence of the trunk perturbation on the arm movement. The perturbation also resulted in a substantial increase in movement time in the Blocked condition. Although PD subjects eventually attained the goal (touching the nose) in Blocked trials, the hand movements became segmented and markedly less smooth (destabilized).

Another aspect of our study investigated individuals' ability to perform two tasks (finger-to-nose test and forward trunk bending) simultaneously during unconstrained movements. In this regard, no between- or within-group differences in onset latencies were noted (see Results section). While delayed reaction time is commonly associated with PD, the magnitude of the deficit varies, depending on task difficulty and the stimulus modality.[24–27] These task dependencies, paired with the lack of demands on reaction time in our paradigm, may explain why we did not observe delayed movement onset latencies in the PD group.

Our primary results may be explained in several ways. One possibility is that PD subjects were impaired because of procedural learning deficits.[28,29] While it is impossible to rule this out entirely, this explanation is unlikely for two reasons. First, when initially trained on the task, PD patients learned the task easily and quickly. Second, analysis across trials showed that there were no learning effects during the experiment for either control subjects or PD patients (see Results section).

Another potential way to interpret the results is that bringing the nose and the finger to each other (e.g., moving targets) posed a challenge to the PD subjects. If this were the case, one could expect to see greater deficits in the Free-trunk condition, in which nose and trunk movement was greatest, which was not observed. One would also anticipate a greater desynchronization in movement onset between the nose and hand in the PD compared to the healthy subjects, which was also not observed. Furthermore, it has been shown that moving targets do not necessarily pose a challenge to PD subjects.[30] Alternatively, one can suggest that, once PD subjects learned to execute the two movement components together, they had difficulty in context-dependent switching from this motor set to one in which it was necessary to dissociate the two movement components. This hypothesis, on the deficiency in rapid context-dependent switching in PD, gains support from three cross-disciplinary findings in upper limb control.

First, other patients with pathological conditions of the BG, asymptomatic Huntington's disease (HD) gene carriers, are deficient in adapting to upper limb perturbations induced during visually guided movement.[31] Although PD and HD are both disorders of the BG, their clinical and neurophysiological manifestations differ. For instance, whereas long latency reflexes (LLR) and somatosensory-evoked potentials (SEP) are largely ab-

sent in HD,[32–35] LLR and SEP are present but abnormal in PD.[9,36,37] Despite these differences, it is interesting to note that both our study and that of Smith and colleagues[31] found the patient groups to be deficient in adaptive control. It is noteworthy that Smith and coworkers[31] did not note this deficit in a group of cerebellar subjects, reinforcing their conclusions of BG involvement.

Second, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxic lesions of the dopamine-containing cells of the BG in nonhuman primates results in markedly degraded context-dependent adaptive control, even in presymptomatic stages.[3] MPTP-treated monkeys in the study by Pessiglione and colleagues[3] reached for food while avoiding obstacles interposed between their start position and the food. Presymptomatic monkeys often exhibited irregular, re-orienting, hand paths bearing a striking resemblance to the hand trajectories observed in our study.

Third, neurophysiological recordings in nonhuman primates show that the BG are not only contextually modulated by sensory input (e.g., by changes in direction, amplitude, and force of movement)[38–40] but can also influence or gate afferent input.[41–43] This function, paired with their vast anatomical connections with cortical and subcortical centers (for reviews, see Middleton and Strict[4] and Turner and Anderson[38]) may place them in a position to participate in context-dependent adaptive control of movement.

The literature reviewed above, taken together with the present findings that the relatively local trunk perturbation had a globally destabilizing effect on the PD subjects' hand movements, implicate the basal ganglia in adaptive control of upper limb movement during changing sensorimotor contexts. It may be that the channeling or gating of sensory information and the high level processing of proprioceptive information and/or the integration with motor commands may be faulty in PD patients and contribute to maladaptive responses. As such, whereas control subjects were able to dissociate and preserve their hand movements from changing conditions related to trunk motion, the segmented hand movements of the PD subjects suggested that they required more processing time to readjust their movement as contextual demands changed (e.g., see Fig. 1, middle and right panels and multiple velocity peaks in Fig. 4A, right). This point is underscored by the markedly elevated movement tardiness index in PD subjects in the trunk-perturbed condition (190 msec), suggesting that these processes may have involved cortical–basal ganglia–thalamic–cortical circuits.

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