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MOTOR IMAGERY OF A LATERALIZED SEQUENTIAL TASK IS ASYMMETRICALLY SLOWED IN HEMI-PARKINSON'S PATIENTS

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Abstract—We examined seven right-handed, asymmetrical (right side affected) Parkinson's disease patients and seven age-matched controls in a manual finger sequencing test using left and right hands in vision, no vision, and motor imagery conditions. All patients displayed motor asymmetry, favoring the left hand. They also displayed *motor imagery* asymmetry, mentally simulating movement more slowly with their right affected hand than with their left hand. Additionally, impairment in mental hand rotation correlated significantly with the imagery asymmetry. These data support two related hypotheses: (a) Motor sequence imagery and execution share common neural structures. (b) The frontostriatal system is among these shared structures.

Key Words: Parkinson's disease; akinesia; basal ganglia; frontostriatal circuitry; motor imagery; sequential task.

INTRODUCTION

Among the common behavioral deficits in Parkinson's disease (PD) are those observed in various sequential tasks. In sequential tasks that involve the execution of a goal directed plan, PD patients are able to generate the correct sequence, but they display increased "thinking" times that are dissociated from their motor response times [30]. When executing non-repetitive motor sequences of different hand postures, PD patients exhibit deficits both in terms of correctness and speed of sequence execution [21]. Similarly, the sequential execution of two motor tasks displayed both a slowing of each task when compared with non-sequential execution, and an increase in the reaction time for the second movement, i.e. the pause between the first and second movement [3]. PD patients also show a deficit in reconstructing the order of presentation of series of drawings, words and designs [40] where each given item in the sequence has no implicit connection to the subsequent item. It has been suggested that the PD patients' impairment in sequential tasks is related to the "internal control" required by the given task [30]. The capacity to perform sequential behavior should be accompanied by a corresponding internal representation of sequential structure that we can characterize in terms of internal states, and transition between states. We can summarize the above data by observing that the self-guided transitions from one internal state to another, both in terms of timing and accuracy (order), is impaired in PD.

This deficit in internally guided state transitions is not restricted to sequential execution.

Indeed, patients are often impaired in tasks in which they must generate a single behavioral state transition based on internal cues. This is seen, for example in shifting between categories in a word fluency test [14]; shifting between sorting category in the Wisconsin Card Sort [32]; or shifting between relevant stimulus attributes in the Stroop test [5]. In most cases, this perseveration (inability to shift) is eliminated by explicitly providing the information that must otherwise be generated internally.

We suggest that this perturbation in internally generated state transitions in PD patients may provide a key to understanding their impairments in sequential behavior. Consider that the execution of a sequence requires a series of transitions from one internal (brain) state to another, where the states encode the successive steps in sequential behavior. A recent model of conditional sequential and non-sequential behavior in primates has suggested that internal state is represented by distributed patterns of activity in cortex, basal ganglia and thalamus. Transitions between states are guided in part by external cue (e.g. vision of the hand completing part of the sequence) and internal cue (e.g. an efference copy of a motor command) influences on cortex. The corticostriatal projection then associates the current state in cortex with both subsequent state (via thalamus) and its corresponding motor output [2, 12, 13].

We can hypothesize that impairments in sequential and non-sequential behavior in PD are due, at least in part, to the failed corticostriatal maintenance of internal states and transitions between these states that encode the succession of steps in sequential behavior, and the single steps in non-sequential behavior. That is, the impairment is not due entirely to the perturbed motor expression of internal states, but also in part to the incorrect generation of these internal states that represent both motor and non-motor events. In order to test this hypothesis, one should perform an experiment which can dissociate the *internal* state control and the *external* expression of a sequential behavior.

Motor imagery tasks offer such a dissociation in which subjects are asked to mentally simulate a given motor action without actual execution. It has been suggested that many of the same neural mechanisms that participate in motor execution are also involved, to some extent, in motor imagery [23]. Several experiments support this view. When comparing actual vs imagined execution, subjects in these studies show similar completion times [9, 10, 33, 34], autonomic nervous system changes proportional to the effort of the action [7, 8, 41] and even performance improvements [42] in both the actual and imagined conditions. Positron Emission Tomography (PET) cerebral blood flow measurements of motor execution have shown that in normal subjects, the execution of a sequential finger movement task activates primary motor cortex, prefrontal cortex (supplementary motor area (SMA) in particular) and the basal ganglia [36, 39]. Other studies have demonstrated the participation of these same structures—with the exception of primary motor cortex—in the mental simulation of motor behavior [11, 19, 27]. Thus we have chosen to compare mental and actual execution of motor tasks in PD patients, in order to dissociate the *generation* of internal states from their *expression* as motor behavior.

METHODS

Patients and control subjects

Patients were selected as having early or mid-stage (duration range 1–7 years) idiopathic, levodopa-responsive Parkinson's disease. The mean age (\pm S.D.) was 56.3 ± 8.0 years, with four males and three females. Chronic anti-Parkinsonian treatment consisted of levodopa (200–800 mg/day, with peripheral levodopa-decarboxylase inhibitor) in all but one case, dopamine agonists in two cases, Deprenyl in one patient, and anticholinergic drugs in

Table 1. Details of the individual patients with Parkinson's disease

Patients	Sex	Age (years)	Duration of illness (years)	Hoehn & Yahr Stage	Treatment
P1	M	44	7	1.5 (on) 2.5 (off)	325 mg l-d, d-s, a
P2	M	55	3	1.5 (on)	375 mg l-d, d-a
P3	F	51	5	1.5 (on)	a
P4	F	62	7	2 (on) 2.5 (off)	800 mg l-d
P5	M	54	1	1.5 (on)	300 mg l-d
P6	M	69	1	1.5 (on)	250 mg l-d, D
P7	F	59	3	1.5 (on)	200 mg l-d

Medication abbreviations: l-d: levodopa/day, d-a: dopamine agonist, a: anticholinergic, D: Deprenyl. The Hoehn & Yahr stage of disease is indicated in all patients while chronically treated ("on"), or for the two fluctuating patients (P1 and P4) in the "on" and in the "off" medication motor state.

two cases. All patients consented to participate in the experiment, and had normal or correct-to-normal vision. Lack of significant intellectual deterioration and depression within normal limits was verified by a psychological interview and testing performed the same day as the imagery testing (data not shown): (1) Wechsler Adult Intelligence Scale—Revised (WAIS—R), (2) Wechsler Memory Scale—Revised, and (3) Wisconsin Card Sorting test (version with 128 cards).

With the goal of testing the degree of parallel perturbation in motor imagery and execution, in this case due to the specific influence of dopamine denervation of the striatum, several characteristics were important for inclusion. First, the presentation of a Parkinson's syndrome with predominant akinesia (the most levodopa-responsive sign in PD) and no tremor; second, essentially unilateral motor signs, which is frequently the case at disease onset [22], in order to compare the effected and unaffected (or less affected) sides. In addition we also investigated in two cases the influence of fluctuations in motor performance under dopamine treatment, in order to compare the two "on" (normakinesia) and "off" (akinesia) motor states. All of the patients in this report were right-handed, and affected on the right side. By studying only right-affected patients we avoid confounding effects of lateralization. The clinical evaluation of the motor state of the patients (as quantified on the Hoehn & Yahr scale [22], and the Unified Parkinson's Disease Rating Scale (UPDRS) [16] were made the same day as the motor imagery testing. The latter was useful in selecting patients with clear asymmetrical extrapyramidal signs, particularly on rapid alternating hand/finger movements. Individual patient data are summarized in Table 1.

A group of seven healthy age-matched volunteers was tested as a control under the same experimental conditions for subsequent comparison with the patients. The control subjects were all right-handed. Their mean age (\pm S.D.) was 54.4 ± 11.7 years, with five males and two females.

Before testing, the patients and subjects were familiarized and trained for imagery instructions with the Movement Imagery Questionnaire [20], and with the Sheehan Mental Imagery Questionnaire [38].

EXPERIMENTS SEQUENTIAL FINGER MOVEMENT AND IMAGERY

Method

This experiment provides a method to determine if the affected non-affected asymmetries in motor sequence execution (visually and non-visually guided) are accompanied by corresponding asymmetries in motor imagery. The experiment was performed with the subject comfortably seated with his arm resting on the table, palm facing upward. In the motor sequence task the subject touched the pad of the thumb with the pad of the first to fourth fingers successively. The subject was instructed to open the fingers wide before each closure, and to perform the closures accurately. The sequence of four finger touches was repeated either three or five times, for each hand, under the following three conditions: (1) motor execution, with vision of the executing hand; (2) motor execution with the eyes closed; and (3) motor imagery (no movement) with the eyes closed.

Each of the 12 combinations (\langle left or right hand $\rangle \times \langle$ three conditions $\rangle \times \langle$ repeated three or five times \rangle) was performed five times for a total of 60 trials. Trials were given in mixed blocks of 15, alternating between the two hands (i.e. 15 left, 15 right, 15 left, 15 right). Half of the subjects started with the left hand, half with the right. Before each trial in a given block, the subject was told the condition (vis, non-vis, imagined) and number of repetitions (three or five). The subjects were continuously instructed (if necessary) to open the fingers as much as possible, and to close them accurately. They were also recorded on video-tape for *post-hoc* confirmation of correct execution. The

motor performance was quantified as a measure in seconds of the completion time for each sequence. Following the condition and number of repetitions instruction, the experimenter verbally gave a ready signal, then a go signal which triggered sequence performance onset in the subject, and also the onset of the timed period (measured by the experimenter) using a hand-held digital chronograph. When the subject completed the (executed or imagined) sequence, he/she gave a verbal stop signal that marked the end of the time period as recorded by the experimenter.

Data analysis

In order to study the affected/non-affected differences between patients and controls in the different conditions, the mean reaction times for each patient and control subject were submitted to a three-way ANOVA with the Hand (left, right) and Condition (Visual, Non-visual and Imagined) as within-subject factors, and Group (patients, controls) as a between-subjects factor.

We also determined: (1) The ratio of execution time vs the number of sequence repetitions (execution rate) in visual (V), non-visual (NV) and imagined (I) conditions in the left and right hands. (2) A measure of the affected/non-affected asymmetry in terms of these rates.

The execution rate, or mean time required to execute the sequence (i.e. inverse of velocity) was calculated separately for the left and right hands, for each of the three conditions (V, NV, I) based on the times required for completing three and five repetitions of the sequence in the three conditions. A measure of the visually guided motor asymmetry was then calculated in terms of the visually guided execution rates for the left (VL) and right (VR) hands. The asymmetry is calculated as $(VL - VR)/(VL + VR)$. This is referred to as the visual asymmetry index, AI_V . This value is positive for asymmetries that favor the right hand, and negative for those that favor the left.

Asymmetry indices were similarly calculated for non-visually guided (AI_{NV}), and imagined (AI_I) movements. A measure of correlation between these values was performed in order to determine if the imagery asymmetry was correlated with the motor asymmetry.

Results

Visual, non-visual and imagined sequence execution. In Fig. 1 we present the combined execution times for three and five sequence repetitions for patient and control groups in the three execution conditions using the left and right hands. The three-way ANOVA revealed a significant main effect for Group [$F(1, 72) = 60.79, P < 0.0001$], with combined completion times being slower for Parkinson's (29.73 sec) than for controls (17.51 sec). Condition was also significant, with completion times for visually guided sequences (20.96 sec) were faster than those for the non-visually guided sequences (23.05 sec), which were in turn faster than

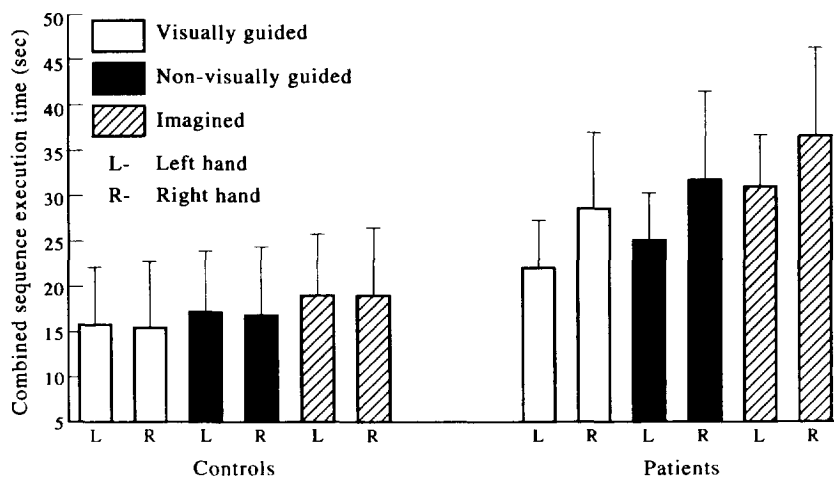


Fig. 1. Sequence execution times for patients and controls. Mean and S.D. for the combined execution times (three and five repetitions) for the visual, non-visual and imagined sequence executions are displayed for left (L) and right (R) hands for the patient and control groups.

those for the imagined sequences (26.86 sec), [$F(2, 72) = 4.81, P < 0.05$]. There was almost a significant main effect for Hand [$F(1, 72) = 3.81, P = 0.05$] with the right hand (25.16 sec) slower than the left (22.10 sec). This rather surprising result is explained by the only significant interaction effect, which was between Group and Hand [$F(1, 72) = 4.18, P < 0.05$]. The controls' completion time for the right hand (17.44 sec) was slightly less (0.15 sec) than that for the left (17.59 sec), while the PD patients completion time for the right hand (32.87 sec) was much greater (6.27 sec) than that for the left (26.60 sec). None of the other interactions approached significance. These results allow us to conclude that the Parkinson patients were significantly slower with their right (affected) hand than with their left (non-affected) hand in all conditions, including imagery, when compared to normal control subjects. We now consider in more detail this affected/non-affected asymmetry.

For all patients, there was an asymmetry in each of the visual, non-visual and *imagined* conditions such that the respective execution with the non-affected left hand was always faster than that with the right-affected hand. These asymmetries are expressed as the asymmetry indices described above for visual, non-visual and imagined cases (AI_V , AI_{NV} , AI_I). Figure 2 displays these ratios for each of seven patients and the control group. Note that for all the patients, the negative values indicate a slowing on the right-affected side. In the control subjects, a non-significant trend towards slowing of the left side with respect to the right was observed.

The asymmetries in sequential *motor imagery* correlated significantly with those for sequential *motor execution*. For the PD patients, the degree of affected/non-affected asymmetry for motor imagery (AI_I) correlated significantly both with visual motor asymmetry (AI_V) ($r^2 = 0.705, P = 0.018$), and the non-visual motor asymmetry (AI_{NV}) ($r^2 = 0.721, P = 0.016$). These linear regressions are presented in Fig. 3.

Motor and imagery asymmetries in "on-off" cases. Both the motor asymmetry and the imagery asymmetry were significantly increased in "off" vs "on" period for the two patients who displayed levodopa-induced "on-off" fluctuations. During the period just preceding the next ingestion of medication, a significant increase in motor impairment (akinesia) was observed. In Fig. 4 we display the asymmetry index results from one of these patients (P1) recorded in both the "off" and "on" conditions. Note that compared to the controls in Fig. 2, this patient is similar to controls with asymmetry indices near zero (i.e. symmetric) when in the "on" condition. In the "off" condition however, he becomes asymmetric not only in the motor execution (visually and non-visually guided) but in the imagined condition as well. The data from the "off" condition for P1 are displayed in Fig. 2.

The second patient (P4), during the "off" condition, was completely incapable of performing the motor sequence with her right-affected hand. At this point the patient was asked to *imagine* performing the sequence with her right hand, and she reported that she was unable to imagine performing the sequence. After taking her medication, the patient was able to perform both the execution and imagery tasks with the affected right hand, and results in the "on" condition were obtained as described above, and presented in Fig. 2.

MENTAL ROTATION OF LETTERS AND HANDS

Method

Mental rotation of letters provides an index of a general mental imagery capacity, while mental rotation of hands appears to rely on a more specific mechanism of motor imagery [33, 34]. These tests were programmed on a MacIntosh computer using MacLabTM software.

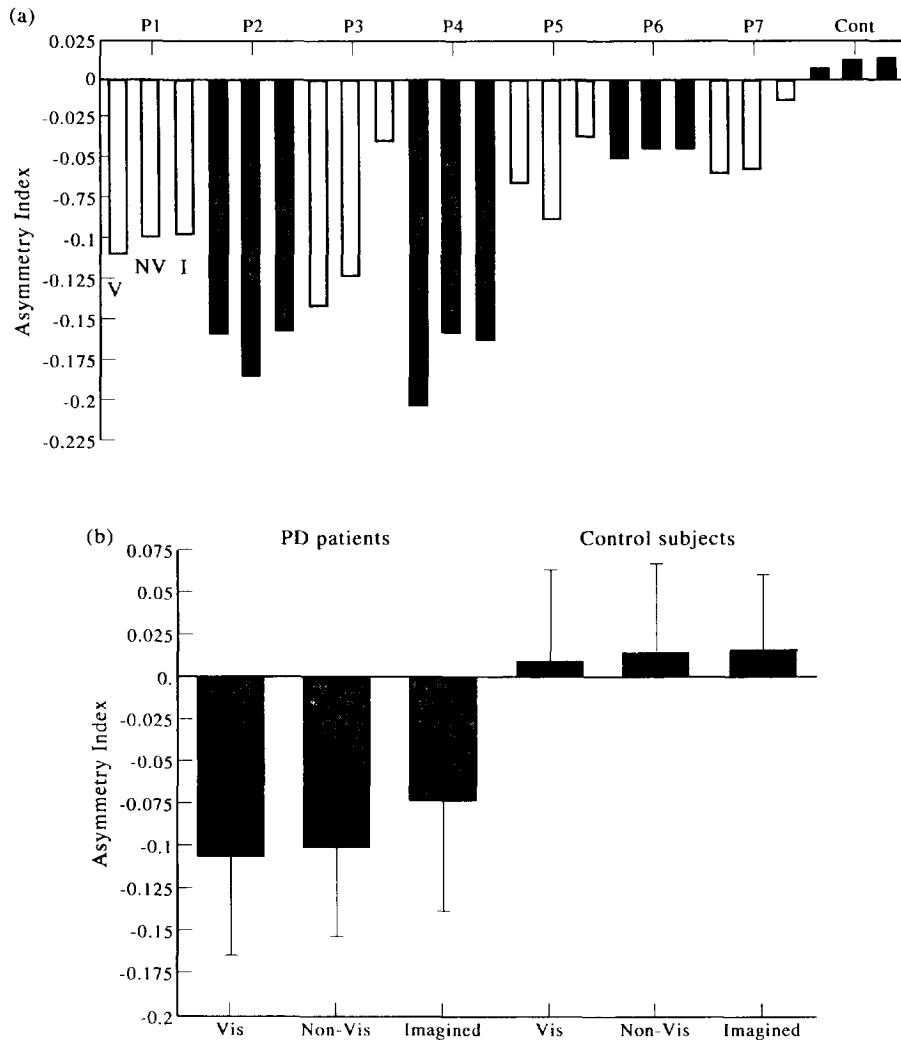


Fig. 2. Asymmetry indices for patients and controls. (a) The visual (V), non-visual (NV) and imagined (I) asymmetry indices are displayed for each of the right-handed patients and the controls (as a group). Increasingly negative values correspond to an increase in the asymmetry favoring the left side. (b) Mean and standard deviations for patients and controls.

Letter rotation. Capital letters (**F** or **R**), 1.5 cm high written in Times (60 points) were presented at the center of the computer screen, after a random delay, in a mirror or normal orientation, with a rotation of between 0 and 315° in 45° increments. The subjects had to determine, as quickly and accurately as possible, if the stimulus was a mirror or normally oriented letter, and respond with the appropriate touch on one of two keys appropriately indicated on the computer keyboard. Three blocks of 32 trials representing all possible cases [(two conditions) × (eight angles) × (two letters)] were presented in random order, with a brief pause between blocks.

Hand rotation. Each stimulus was composed of a single line drawing figure of either a right or left hand, 5.45 cm high and 2.20 cm wide, presented on the screen. The hands were presented in "palm" or "back" version at angles between 0 and 315° at 45° intervals. Palm and back versions were easily visually distinguished by the lines of the palm, and the finger nails of the back, respectively. The subject had to determine as quickly and accurately as possible if the stimulus was a left or right hand, and indicate the response by pressing the appropriately marked key on the keyboard. Three blocks of 32 trials were presented. In each block all possible combinations (2 hands × 8 angles × 2 configurations) were presented in random order.

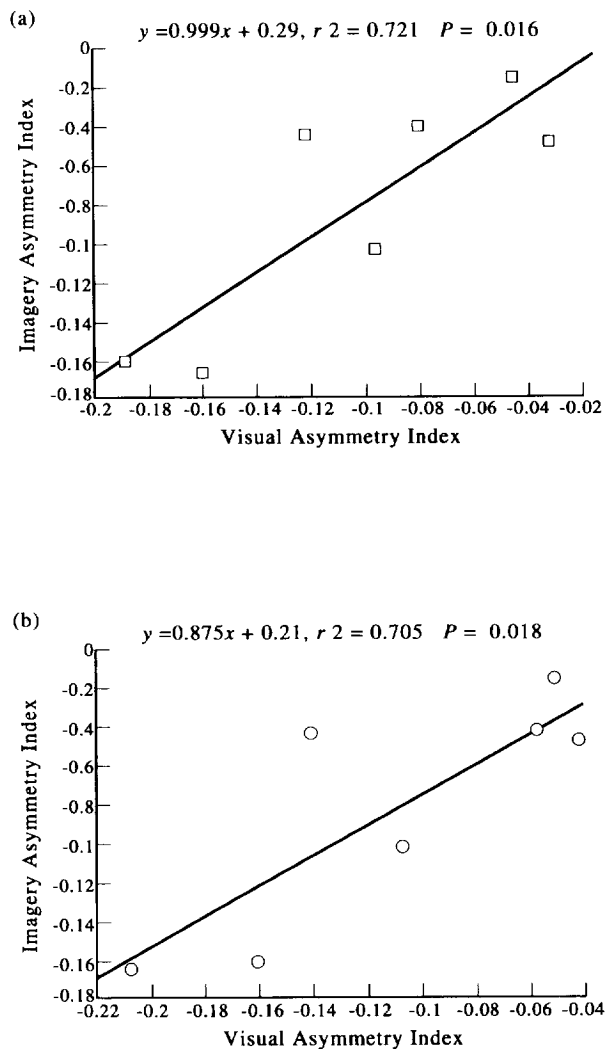


Fig. 3. Comparison of imagery asymmetry with visual and non-visual asymmetries. (a) Display of the linear regression performed on the imagery and non-visual asymmetry indices. (b) Display of the linear regression performed on the imagery and visual asymmetry indices.

Data analysis

Reaction time values were recorded for correct responses at 0, 45, 90, 135, 180, 225, 270 and 315° rotations. The means and standard deviations were calculated. Reaction time values greater than two standard deviations from the mean were rejected as due to distraction or loss of attention, and thus meaningless for comparison purposes. One patient (P3) was excluded from subsequent comparison because of excessive (>50%) errors in hand rotation responses. Comparison of Patient and Control group means are presented in Fig. 5.

The mean RTs for each patient and control subject in the hand and letter rotation tasks were submitted to a three-way ANOVA with Object (Hand, Letter) and Angle (0°–315° in 45° increments) as within-subject factors and Group (patients, controls) as between-subject factors. Separate ANOVAs for hand and letter rotation were also performed to examine the interactions between the stimuli (left-right for hands, mirror-normal for letters), angle and group.

In an additional analysis, the values for 45° and 315°, 90° and 270°, and 135° and 225° were combined as they are clockwise/counter-clockwise rotations of the same extent. This yielded a set of values for 0°, 45°, 90°, 135° and 180° rotations. A linear regression was then performed on this set to determine the time per degree of rotation (the slope of

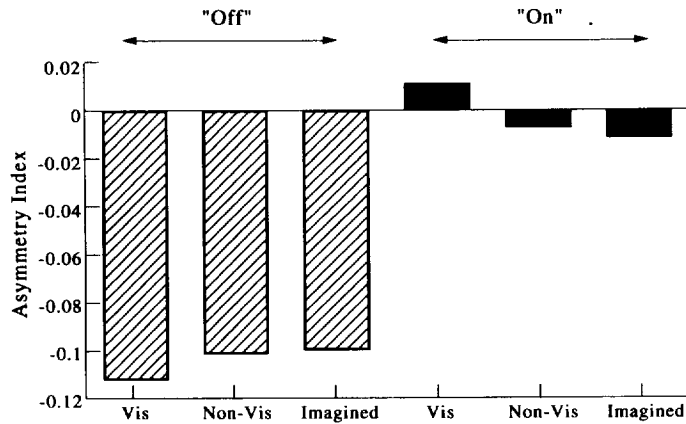


Fig. 4. Asymmetries in "on" and "off" conditions in a single patient. The visual, non-visual and imagined asymmetry indices are displayed for patient 1 in the "off" and "on" conditions.

the regression line, called H_S for hand rotation, L_S for letter rotation), and the minimum time (the intercept). The correlation between hand and letter rotation rates (H_S and L_S , respectively) was computed. A measure of the relative discrepancy between hand and letter rotation rate was calculated as $D_{L,H} = L_S/H_S$. The correlations between the rotation rate parameters (H_S , L_S and $D_{L,H}$) and the sequencing parameters (AI_V , AI_{NV} , AI_I) were then investigated.

Results

For the three-way ANOVA with Object (Hand, Letter) and Angle (0 – 315° in 45° increments) as within-subject factors and Group (patients, controls) as between-subject factors there were significant main effects for each of these factors. Hand rotation (2325 msec) was slower than letter rotation (1214 msec) [$F(1, 160) = 238$, $P < 0.0001$]. RTs increased with the angle of rotation with the minimum at 0° from vertical (1406 msec) to a maximum at 180° (2341 msec), [$F(7, 160) = 9.39$, $P < 0.0001$]. Parkinson's patients' RTs were slower (1925 msec) than controls' (1614 msec) [$F(1, 160) = 18.73$, $P < 0.0001$]. There was a smaller but significant interaction between Group and Object [$F(1, 160) = 6.32$, $P < 0.05$]. This showed that for PD patients the increase (982 msec) in RT between letter (1461 msec) and hand (2389 msec) rotation was less than the increase (1192 msec) between letters (968 msec) and hands (2260 msec) for controls.

In order to determine if there was a difference in hand rotation times for left and right hands we performed a three-way ANOVA on Hand (left, right) and Angle as the within-subject factors and Group (PD, control) as the between-subject factor. Parsons [33] has previously shown that in right-handed subjects, there is a significant main effect for handedness of stimulus (left, right) hand ($P < 0.01$), but that this effect can be masked by the more significant effects of stimulus type (palm, back $P < 0.001$), and angle ($P < 0.001$). In that study [33] the maximum RTs that preserved this left–right difference were in response to palms rotated clockwise 120° , and so we used palm views sampled at (clockwise) 90° and 135° for this test.

There was a significant main effect for Rotation, with 90° (2257 msec) shorter than 135° (2962 msec) rotations [$F(1, 40) = 7.13$, $P < 0.02$]. Hand also showed a significant main effect, with the left hand (2257 msec) faster than the right hand (2961), [$F(1, 40) = 7.13$, $P < 0.02$]. The only other significant effect, an interaction between Hand and Group, [$F(1, 40) = 5.44$,

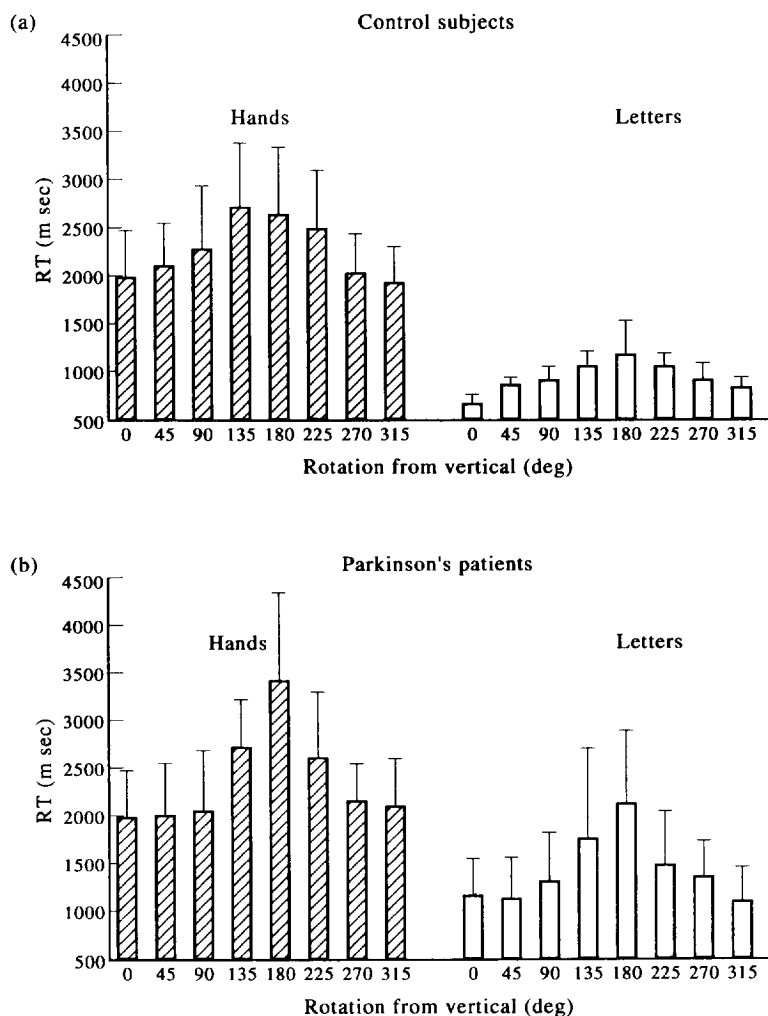


Fig. 5. Reaction times (group mean and S.D.) for hand and letter rotation. (a) Control subjects and (b) patients.

$P < 0.05$], revealed that while control subjects' right-hand RTs (2473 msec) were slightly (13 msec) faster than their left-hand RTs (2486 msec), PD patients showed a strong reversal of this effect. Their right-hand RTs (3450 msec) were much longer (1423 msec) than their left-hand RTs (2027 msec).

In order to determine if this slowing in right-hand rotations in PD patients was due to some artifact related to the 90 and 135° rotations, we performed a three-way ANOVA on the letter rotation data, using Version (mirror, normal) and Angle (90, 135) as the within-subject factors and Group (PD, control) as the between-subject factor. The only significant effect was a main effect for Group, with RTs for the PD patients (1777 msec) slower than those for the controls (1001 msec) [$F(1, 40) = 6.39$, $P < 0.02$]. The lack of other main effects or interactions tells us that the left-right hand effect was not due to an artifact.

Relation of mental hand and letter rotation to the sequencing task

The most striking observation was a significant correlation between the letter–hand rotation rate discrepancy (D_{LH}) and the three asymmetry indices for finger sequencing (AI_V , AI_{NV} , AI_I). For all patients and the control group, the reaction times for hand and letter rotation could be described by a linear regression with probability of error always $P < 0.055$. The regressions are summarized in Tables 2 and 3 for hand and letter rotation, respectively. This allows us to consider the slope of the regression line as a measure of time per degree of rotation.

The values H_S and L_S specify the rate of rotation in milliseconds per degree for hand and letter rotation respectively. We examined the relation between H_S and L_S and found no significant correlation between them. We then quantified the discrepancy between hand and letter rotation rate as $D_{LH} = L_S/H_S$. Based on the idea that motor imagery is more involved in hand rotation than in letter rotation [33], we can consider that D_{LH} provides an index of motor imagery capacity. This letter/hand rotation discrepancy index D_{LH} was found to correlate significantly with the affected/non-affected asymmetry indices for the visual, non-visual and imagined finger sequence task (AI_V , AI_{NV} , AI_I , respectively). The correlation parameters are shown in Table 4.

Table 2. Linear regression parameters for letter rotation

	Constant	Slope— L_S (msec/deg)	R^2	P
Controls	704	3.298	0.98	0.001
P1	779	3.198	0.77	0.049
P2	1029	6.104	0.85	0.026
P4	949	4.796	0.79	0.043
P5	725	2.389	0.93	0.008
P6	1681	6.313	0.92	0.010
P7	860	8.229	0.78	0.047

Table 3. Linear regression parameters for hand rotation

	Constant	Slope— H_S (msec/deg)	R^2	P
Controls	1858	4.040	0.92	0.009
P1	1621	3.833	0.90	0.013
P2	1936	14.296	0.79	0.042
P4	1191	12.067	0.87	0.020
P5	2129	2.842	0.76	0.053
P6	2077	7.324	0.91	0.011
P7	1249	8.767	0.79	0.043

Table 4. Linear regression parameters for letter/hand discrepancy and visual, non-visual and imagined asymmetries

	Constant	Slope	R^2	P
D_{LH} vs AI_V	-0.287	0.25	0.88	0.005
D_{LH} vs AI_{NV}	-0.264	0.22	0.86	0.008
D_{LH} vs AI_I	-0.269	0.26	0.88	0.006

LOWER TO UPPER CASE LETTER IMAGERY

Method

This test provides a standard measure of mental imagery capacity. Lower case characters (same size and font as above) were presented in the center of the screen. The subject was asked to imagine the corresponding upper case character and decide if it was composed entirely of straight lines (e.g. H), or at least one curve (e.g. R). The subject responded by touching the appropriately marked keys on the computer keyboard. Eight "straight" (t, v, f, k, l, z, e, m) and eight "curved" (j, d, q, r, o, b, p, g) letters were presented twice each in a block of 32 trials. Each presentation was preceded by a fixation point for a random interval. This test was adapted from the Letter corner classification used by Farah *et al.* [17].

Data analysis

This test yields two parameters of interest. The percentage of correct responses provides an index of the capacity to imagine the upper case letter corresponding to the visually presented lower case letter, and the reaction time provides an index of this mechanism's rate. The mean reaction time and percentage correct was calculated and compared with values for the asymmetries computed above.

Results

Performance on the lower-to-upper case imagery test, both in terms of percentage correct and reaction time, did not differ significantly between patients and controls (data not shown). This indicates that any patient-control differences in motor imagery tasks are likely to be related specifically to motor imagery, rather than to a generalized impairment in mental imagery for the patients.

DISCUSSION

The goal of this study was to determine if there is a systematic relation between deficits in motor execution and motor imagery in Parkinson's disease. This question was motivated by our hypothesis that the frontostriatal system is involved in the control of internal state, and transitions between internal states that encode both sequential and non-sequential movement execution [2, 12, 13]. Such a state transition mechanism would be required not only for motor execution of single movements and movement sequences, but also for their mental simulation, since actual and simulated execution entail essentially the same trajectory of internal states. The anatomical pathway for this state transition mechanism, which is impaired in PD, might include the "complex" and "motor" loops interconnecting frontal cortex, basal ganglia and thalamus as described by Alexander *et al.* [1]. Indeed, Saint-Cyr *et al.* [37] have demonstrated that the internal state control necessary for sequential procedural learning is impaired in PD patients.

Our observation of a significant correlation between affected/non-affected asymmetries in motor execution and motor imagery in PD patients indicates that these two processes are similarly affected in Parkinson's disease. According to our working hypothesis that state control in execution and imagery share a number of common brain structures and mechanisms [6, 23], both execution and imagery will be asymmetrically affected in asymmetrical PD patients precisely because both processes rely on the same function—internal state management—which requires an intact frontostriatal system. Hence these results support our hypothesis.

Previous studies of mental rotation of images of hands vs letters have concluded that the preferred strategy in this task is to imagine moving one's own hand, as opposed to rotating the stimulus to a standard position as used by people discriminating normal from mirror reversed letters [33]. We found that in conditions with maximal RTs (palm rotated 90° or 135° CW) the patients were significantly slower for mental rotation of the right (affected)

hand than for the left hand with respect to controls. This agrees with our data in the finger sequencing study showing that the affected right hand was slower in PD patients both for execution and imagery, indicating that motor imagery and execution share common underlying functions. This also suggests that in hemi-PD, operations that involve state transitions related to motor representations (for execution or imagery) will be affected asymmetrically relative to state transitions related to non-motor representations (e.g. letter rotation).

Indeed, a recent study [15] testing mental rotation of Arabic numerals and stick figures found no difference between PD patients (including those with lateralized symptoms) and controls. This study [15] utilized extensive pre-testing familiarisation and training sessions that included 24 practice trials for each numeral-orientation-version combination with feedback on accuracy after each trial. It is likely that our findings of an increase for PD patients vs controls in letter rotation may be related to our relatively “naïve” testing condition in only which two examples and three practice trials were presented prior to testing.

In addition we can consider that our index D_{LH} provides a measure of motor imagery with respect to non-motor mental imagery as it provides a ratio of letter rotation vs hand rotation velocities. The positive correlation between this value and that for the deficit (asymmetry) in both motor execution and imagery of the sequence task is again positive evidence that deficits in motor execution and imagery in PD are related.

In this study, we have developed a manual sequencing protocol that dissociates the internal representation of a sequential motor act from its external expression. We saw an increase in execution times in the non-visual vs visual and imagined vs non-visual conditions for the normals, and a greater increase, respectively for the patients. This agrees with the observation of Klockgether and Dichgans [25] that PD patients are more dependent on visual information than are normals. By observing PD patients’ performance in motor imagery we extend this result to say that they are more reliant on all peripheral feedback than are normals.

One criticism that can be raised against this study is that a form of order effect may contaminate the patients’ motor imagery times. Since the imagery trials are mixed with execution trials, the patients may memorize the execution times and reproduce them during imagery. We mount two arguments against this criticism. First, Parsons [34] has recently demonstrated in experiments where some subjects perform actual hand rotations prior to mental hand rotation, that “Left–right judgement times were unaffected by subjects first performing real movement to (the) stimuli” (p. 713). Second, our observation of slowing of the affected hand in mental hand rotation for PD subjects occurred in a test where no overt movements could contaminate the covert imagery.

In addition we note that for the non-affected (left) hand the patients are slower than controls. While all of our patients display an asymmetric motor deficit, they are also impaired, with respect to normal controls, on their non-(or less) affected side. The presentation of a pure unilateral deficit is quite rare. More common, as in our patients, is a predominantly unilateral deficit that still displays some impairment on the non-affected side.

Our results show that, with respect to frontostriatal dysfunction in PD, the internal representation (imagery) and external expression (movement) of motor sequences are affected in parallel. This study then agrees with the observations that among the functions of the basal ganglia is the conditional selection of response based on internal state [5]. In addition, however, we conclude that the basal ganglia not only respond to the internal state,

but also participate in maintaining the internal state, and in controlling the orderly succession of transitions from one internal state to the next.

Regional cerebral blood flow studies using PET imagery support this idea. In a task involving object grasping, Decety *et al.* [11] compared activation during motor imagery vs observation of a motor task, subtracting activity during visual inspection of the object. They noted significant bilateral increases in activation of the caudate nucleus and premotor cortex in normal subjects during motor imagery as compared with their activation during movement observation. During sequential finger movements, Roland *et al.* [36] observed bilateral activation in basal ganglia. This indicates that the basal ganglia are not only involved in the initiation of movement, but again, in the ongoing control of internal state during sequential movement.

Similar studies of visual imagery have demonstrated that many of the same structures that are required for visual perception are also involved in visual imagery [18, 26], though there exist neurological conditions that impair certain forms of visual imagery while leaving visual perception intact [17]. The general message is that the internal simulation or the actual expression of external (perceptual or motor) events share an overlapping neurophysiological basis.

Our findings emphasize the close relationship that links the frontostriatal-related deficits in PD patients and the lesions of the nigrostriatal dopaminergic system. Post-mortem studies in PD patients with unilateral onset of symptoms have shown greater degeneration of substantia nigra compacta cells contralateral to the side of the body affected initially [24]. Conversely, *in-vivo* visualisation with PET of the presynaptic dopaminergic system using fluoro-18-F-Dopa as the tracer, revealed bilaterally reduced putamen tracer uptake, activity being more depressed in the putamen contralateral to the more affected limbs [4, 28, 31]. A significant correlation was noticed between depression in striatal fluoro-18-F-Dopa uptake of PD patients and their degree of locomotor disability [4, 28]. The present study is in line with these findings, notably the results obtained in the two PD patients with levodopa-induced motor fluctuations. In addition, it clearly demonstrates that motor and imagery asymmetry are closely related since they significantly and proportionally increase in “off” as compared to “on” period. Interestingly, other dopamine-related non-motor cognitive impairments have been recently disclosed in PD patients [29]. These conclusions can be further examined by PET studies on akinetic hemi-Parkinsonian patients with the same or a similar paradigm. We would predict asymmetries in frontostriatal cerebral blood flow changes, depending upon the side (affected or not affected) but less so upon the condition of the motor task (executed or imagined).

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