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Impairment of context-adapted movement selection in a primate model of presymptomatic Parkinson's disease

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Summary

The MPTP model allows the presymptomatic stage of parkinsonism to be studied in primates and hence specific behavioural manifestations of moderate nigrostriatal denervation to be identified. On the basis of the physiological literature, we hypothesized that depletion of striatal dopamine could impair the selection of context-relevant habits. To examine this hypothesis, we trained three African green monkeys to perform a simple reach-and-grasp task, including three contexts differing only in terms of the presence and position of transparent obstacles. At the end of training, the analysis of reaching trajectories showed that intact monkeys had built a repertoire of movements, from which they could select the appropriate one depending on the context. In the course of MPTP intoxication (0.3–0.4 mg/kg every 4–5 days) and before parkinsonian motor symptoms appeared, the reaction time (RT), movement time (MT) and variability of reaching trajectories increased in all monkeys. Frequently, the initial direction was not adapted to the context, and consequently the movement was either corrected online or restarted under visual assistance. These non-adapted trajectories appeared to be the main reason for the increase in both RT (because of difficulty in selecting) and MT (because of the need to make corrections). These observations indicate that moderate MPTP-induced dopamine depletion results in a deficit in the selection of context-adapted movement, which is compensated by corrections using either proprioceptive or visual feedback. Similar behavioural disorders might therefore occur in the presymptomatic stage of human Parkinson's disease.

Keywords: Parkinson's disease; monkey; basal ganglia; movement selection; procedural learning

Abbreviations: C–H = context–habit; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MT = movement time; preS = presymptomatic; RT = reaction time

Introduction

The cardinal features of Parkinson's disease are gross motor symptoms: akinesia, rigidity and tremor. These motor symptoms usually become prominent after a long course of dopaminergic denervation within the basal ganglia, complicated by several lesions outside the basal ganglia (Javoy-Agid *et al*., 1984; Dubois *et al*., 1992; Hirsch and Herrero, 1997). The neurotoxic properties of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) provide an opportunity to study presymptomatic (preS) monkeys with moderate dopamine depletion restricted to the striatum (Schneider, 1990). Cognitive deficits have been reported to precede motor symptoms in progressive MPTP-induced parkinsonism, not only in monkeys (Schneider and Kovelowski, 1990; Slovin *et al*., 1999) but also in humans (Stern *et al*., 1990; Cooper *et al*., 1991). The motor symptoms may therefore be secondary disorders that mask a primary deficit due solely to striatal dopamine depletion. Such a primary deficit could affect two functions currently attributed to the basal ganglia: namely, procedural learning, which refers to the progressive and implicit acquisition of a context-relevant habit, and/or action selection, which refers to the motivated choice of a context-relevant movement set.

A role of the basal ganglia in procedural learning was endorsed by experiments in rodents and monkeys, which showed that specific striatal ablation or inactivation severely impaired stimulus–response learning (McDonald and White, 1993; Packard and McGaugh, 1996; Miyachi *et al*., 1997) and that significant changes of neuronal activity occurred within

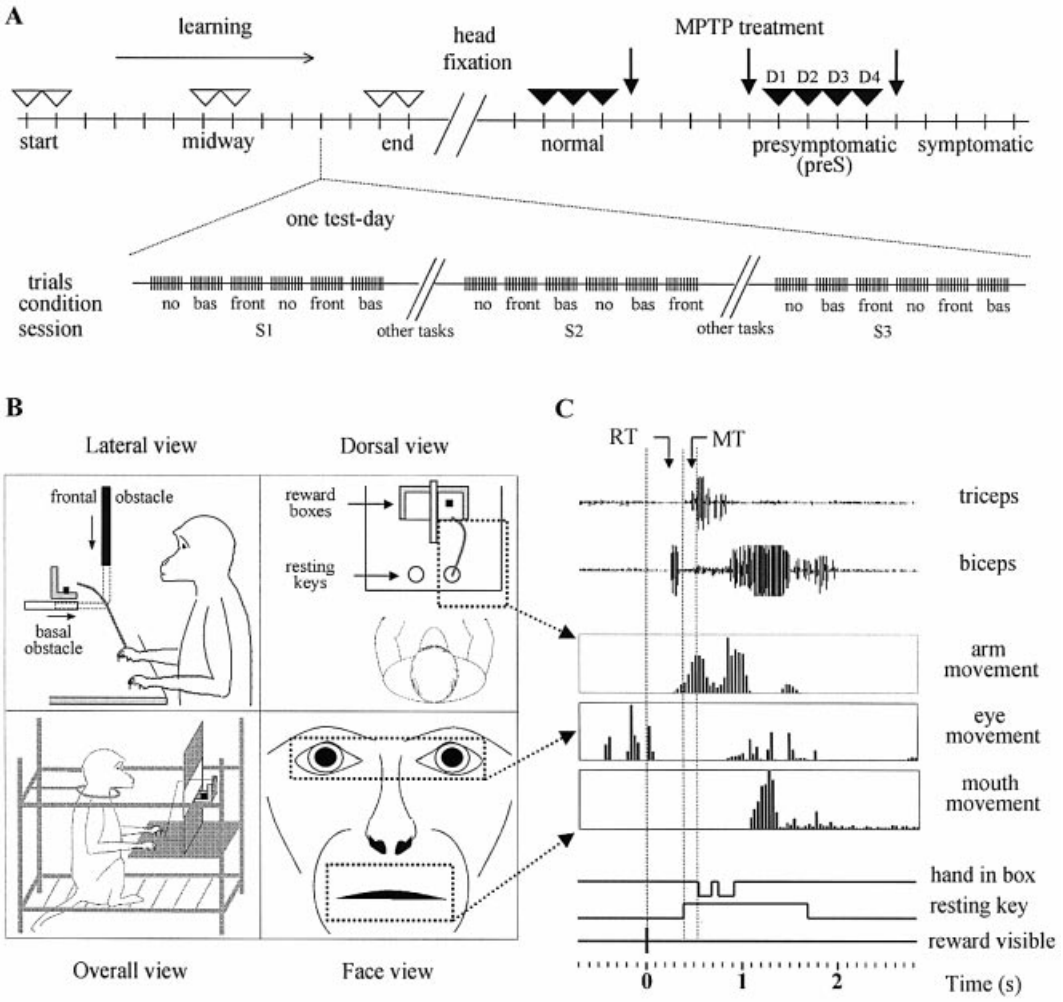

Fig. 1 Experimental procedure. (**A**) Successive stages of data collection (Monkey M). Days are marked by a small vertical bar and test-days included in the results are marked by a triangle. In one test-day, the monkey performs three experimental sessions (S1–S3) containing six blocks of 10 trials. Each block corresponds to one of three conditions: no = no obstacle; bas = basal obstacle; front = frontal obstacle. The schedule comprises two periods, task learning and MPTP treatment, separated by a surgical intervention allowing head fixation. A first comparison (white triangles) concerns the successive learning stages (start, midway, end), and a second comparison (black triangles) concerns the normal and preS stages. The presymptomatic (preS) stage refers to a period following two or three MPTP injections (black arrows) and lasting 3 or 4 days (from D1 to D4). The preS stage is immediately before the injection that produces parkinsonian motor symptoms. (**B**) Schematization of a video recording with four views collected by a quadravision system. The overall view is used to control the posture of the monkey. The face view and the dorsal view are used to analyse the kinematics of eye and arm movements, respectively. The lateral view is used to draw the hand trajectory from the resting key to the reward box. (**C**) Three techniques employed to analyse a single trial. (*Bottom*) Event markers of the trial, starting with reward introduction and finishing with hand returned to the resting key. The interval between reward appearance in box and key release defines the reaction time (RT), and the interval between key release and hand insertion in box defines the movement time (MT). (*Middle*) Quantity of movement measured on different body parts. The three successive peaks of hand recording correspond to the movements directed to the box, to the mouth and back to the key, respectively. (*Top*) Electromyographic recording of two antagonist muscles in the arm. The movement from the resting key to the box requires two successive bursts of activity, the first one in the biceps and the second one in the triceps.

the striatum during learning of new stimulus–response associations (Aosaki *et al*., 1994; Tremblay *et al*., 1998; Jog *et al*., 1999). A role of the basal ganglia in action selection was suggested by their anatomical relations (Mink and Thach, 1993), suitable not only for the detection of contextual cues (via afferent fibres from a wide range of cortical areas) but also for influencing actions (via efferent fibres to movement-related structures in the frontal cortex and brainstem). Both context-related (Hikosaka *et al*., 1989*a*; Schultz and Romo, 1992; Graziano and Gross, 1993) and movement-related (DeLong, 1973; Hikosaka *et al*., 1989*b*; Romo *et al*., 1992) activities have been recorded from striatal neurons in monkeys.

Although computational modelling tends to treat procedural learning (Dominey, 1995; Houk *et al*., 1995) and action selection (Berns and Sejnowski, 1996; Gurney *et al*., 2001)

separately, these functions may not be mutually exclusive. More precisely, if learning enhances the strength of connection between one contextual cortical coding and one basal ganglia output, it could facilitate the selection of the same output on any subsequent occurrence of the same context. As a reward predictor (Schultz *et al*., 1993, 1997), striatal dopamine is a good candidate to link the two functions. Indeed, reward-related dopamine release is well suited to the mediation of (i) a short-term widespread tuning of corticostriatal transmission (Brown and Arbuthnott, 1983; Garcia-Munoz *et al*., 1991) and (ii) a long-term focused reinforcement of active corticostriatal synapses (Wickens *et al*., 1996; Calabresi *et al*., 2000). Depletion of dopamine could therefore impair both the selection of context-adapted habits and the reinforcement of context–habit (C–H) associations.

The MPTP model is suitable for the testing of this hypothesis, since it allows the stabilization of motor habits to be controlled before the inducement of dopamine depletion. By analysing the preS period, we sought to dissociate the putative impairment of movement selection from purely motor symptoms. In this experiment, normal monkeys were trained to build a repertoire of three reaching movements, corresponding to three contexts that differed only in terms of the presence and the position of transparent obstacles. The direct reaching movement (without any obstacle) was used by Schultz *et al*. (1989) to show that reaction time (RT) and movement time (MT) are delayed in hypokinetic MPTP-treated monkeys. We extended these classical measures to further investigate movement preparation and movement execution. For the preparation process, we measured the initial slope of reaching trajectories to determine whether the selected movement was adapted to the condition. For the execution process, we analysed hand kinematics to determine whether the reaching movement was restarted, and we recorded ocular saccades to determine whether the movement was visually assisted. Using these different analytical tools, we verified that the movements performed by trained intact monkeys were selected on the basis of internal representation (with adapted initial slope) and executed without the use of external feedback (without ocular saccades). We then tested in the same monkeys, at a preS stage of MPTP-induced parkinsonism, the presence of (i) selection of movements non-adapted to the context, and (ii) correction of ill-selected movements based on external feedback.

Parts of this study have already been published in abstract form (Pessiglione *et al*., 2001).

Methods

Subjects

Experiments were conducted on three male African green monkeys (*Cercopithecus aethiops sabaeus*) weighing 4–6 kg, provided by the Barbados Primate Research Center, Farley Hill, Barbados, West Indies. Care and treatment of these monkeys were in strict accordance with National Institutes of Health guidelines (1996) and the recommendations of the EEC (86/609) and the French National Committee (87/848). Monkeys were trained daily to perform a battery of behavioural tasks, including the simple reach-and-grasp task with obstacle detour reported in the present study. Apart from this 3 h testing session, the animals were housed in individual standard primate cages ($0.8 \times 0.9 \times 1.2$ m). In the evening, they were given a limited amount of fruit; high-protein pellets were available unrestrictedly and freely.

Experimental schedule

The diagram in Fig. 1A summarizes the successive stages of the experiment.

In the course of the learning period, the monkeys became familiar with the testing apparatus and acquired stable performance in the different tasks. We recorded in Monkey M the progressive learning of the reach-and-grasp task, divided into three successive 2 day periods: the first period, when obstacles were introduced (start period), a midway period, and the period when behavioural performance was stable (end period). After learning and before MPTP treatment, surgery was performed, under fluothane anaesthesia, in order to fasten over the skull of the animal a recording chamber for the electrophysiological studies, and two metal cylinders allowing head fixation on the primate chair. For EMG, insulated stainless steel wires (seven strands) were implanted in the biceps, triceps and hand extensor of the two arms. The wires ran subcutaneously from the muscles to a connector fixed behind the recording chamber. A retraining period followed the surgical operation, to make sure that the monkeys' behaviour was still accurate and stable. At the end of this period, behavioural data were collected for 1 week, but only for the 3 days preceding the first MPTP injection were they fully analysed and included in the results to characterize the normal state.

The three animals then received 0.3–0.4 mg/kg of MPTP every 4–7 days by intramuscular injection under light ketamine anaesthesia. Behavioural data were collected for 3 or 4 days after each injection. To determine the preS stage, we preferred to use a behavioural marker (the appearance of motor symptoms) rather than a given dose of MPTP, because of the well-known variability of sensitivity between monkeys (Elsworth *et al*., 2000). Hereafter, the term 'motor symptoms' refers to the clinical signs used to diagnose Parkinson's disease, namely akinesia, rigidity and tremor. The assessment of these motor symptoms was supervised by an experienced neurologist (D.G.). In order to detect akinesia, spontaneous behaviour was assessed every morning for 30 min using an activity counting system (Vigie Primates; see below): first, in the home cage before anyone entered the animal quarters; secondly, in the experimental chair before starting the experiments. The presence of tremor was checked in different situations (both in the home cage and in the chair, both spontaneously and during fruit juice ingestion), and the

presence of rigidity was assessed by joint manipulation. MPTP injections were repeated until the first motor symptoms were observed. For the purposes of this study the term 'presymptomatic stage' (preS) refers to the data collection period (lasting 3–4 days) preceding the injection that led to the first motor symptoms.

Testing apparatus

Animals were seated in a standard primate chair, facing two small boxes fixed at shoulder height and separated by a central transparent plate (Fig. 1B). This central plate helped (but did not force) the subjects to learn that they were not allowed to reach for either box with the contralateral hand. Before surgery, monkeys were attached by a rigid collar that left the head free to move; after surgery, the head was restrained in the direction of the boxes. Two transparent Plexiglas plates were used as obstacles to prevent a direct reaching movement; one plate was in the vertical plane (referred to as the frontal obstacle) and one was in the horizontal plane (referred to as the basal obstacle). Several detectors were added to record event markers: photoelectric cells were placed in the box in order to detect the appearance of the reward (i.e. when it became visible to the monkey) and hand insertion (when the subject's fingers entered the box); touch-sensitive detectors were placed under resting keys in order to detect movement onset.

Behavioural tasks

To start a trial, the subject had to grasp lightly the two resting keys (one in each hand). After a variable delay, the experimenter introduced the reward (a piece of apple) into one of the two boxes. The subject was allowed to retrieve and eat the reward as soon possible, and then to start the next trial. If the subject failed to retrieve the reward within ~10 s, the trial was aborted and repeated later. The experimenter was seated behind an opaque screen that hid his movements, thereby preventing the subject from anticipating the introduction of the reward. The bait was placed variously in either the left or right box, so as to prevent the subject from guessing which hand to use, with a maximum of three consecutive trials on the same side.

The task included three conditions: the no-obstacle condition (allowing a direct reaching movement), the basal-obstacle condition (imposing a detour over the obstacle) and the frontal-obstacle condition (imposing a detour under the obstacle). The condition was switched after blocks of 10 trials (Monkey M) or five trials (Monkeys R and G); thus, for a given hand, one block consisted of four to six trials (Monkey M) or two or three trials (Monkeys R and G).

Within a session, six blocks were counterbalanced in either of the following two orders: (i) no obstacle/basal obstacle/frontal obstacle/no obstacle/frontal obstacle/basal obstacle; (ii) no obstacle/frontal obstacle/basal obstacle/no obstacle/basal obstacle/frontal obstacle.

During training, the monkeys performed five sessions in one day. In the normal and preS stages, the number of sessions per day was only two (Monkey M) or three (Monkeys R and G). These sessions were alternated with other tasks, not reported in the present study.

Data collection

The following data were collected on-line during experimental sessions using Spike 2 software (CED, Cambridge, UK): (i) the EMG activity of the biceps and triceps (Fig. 1C, top); and (ii) the markers of reward appearance, hand movement onset and hand insertion in the box (Fig. 1C, bottom). From these event markers we deduced reaction time (RT), defined as the time between reward appearance in the box and key release, and movement time (MT), defined as the time between key release and hand insertion in the box. RTs >1 s and MTs >2 s were excluded as marginal values due to animal distractibility. As the biceps is the first muscle to be activated during initiation of the reaching movement (Schultz *et al*., 1989), we used the biceps EMG activation to distinguish between pre-EMG and post-EMG time within RT.

Other data were collected off-line from video recordings by a quadravision system designed to visualize any behavioural sequence from four different views, as illustrated in Fig. 1B.

First, we checked whether the monkeys initiated their reaching movement with the hand ipsilateral to the baited box. We counted as an error in hand selection each time that the contralateral hand released the resting key after the reward appearance and before the onset of the ipsilateral hand movement.

Secondly, we traced the reaching trajectory (executed during MT) of the middle finger second joint, from the resting key to the box entrance. For this reconstruction, we used Synchrotracker software (Viewpoint, Lyon, France), designed to display slow-motion video in the background and to convert the drawing made by the observer into numerical coordinates. Three observers participated in this reconstruction and obtained similar results. Both dorsal and lateral views (for examples see Fig. 1B) were studied but, since much of the information they provided was duplicated, only the lateral view was further analysed, as it was considered more relevant, given the position of the obstacles. From the numerical coordinates we calculated the initial slope of the trajectories. For the obstacle conditions, the initial slope served as a criterion to distinguish between adapted trajectories (with initial slope anticipating the detour) and non-adapted trajectories (with initial slope directed towards the obstacle). For a given obstacle condition, a trajectory was classified as (i) adapted if the initial slope was outside the 95% confidence interval (mean ± 1.96 standard deviations) of trajectories executed in the post-learning normal state in the no-obstacle condition; or (ii) non-adapted if the initial slope was outside the 95% confidence interval (mean ± 1.96

standard deviations) of trajectories executed in the post-learning normal state in the same obstacle condition.

Due to this demanding statistical criterion, many trajectories failed to be included in these categories; they are hereafter referred as 'unclassified'.

Thirdly, we analysed the kinematics of the reaching movement using Vigie Primates software (Viewpoint), designed to convert analogue signals from video recordings to a digitized image that can be displayed on a computer screen. The sampling rate (25 Hz) allowed each image recorded by the video cameras (every 40 ms) to be converted. Between two successive images, the software counts the number of pixels that have changed their brightness. This arbitrary number indicates a movement amplitude for a 40-ms time bin, and thus reflects movement velocity. Within the digitized image, it is possible to restrict the counting to several windows. Examples of window positioning over different body parts are shown in Fig. 1B, and the corresponding results are in Fig. 1C (middle). We used the eye window to detect ocular saccades and the arm window to characterize the reaching movement. For the latter, we defined a split movement as a movement containing at least two velocity peaks within the MT.

Statistical analysis

To confirm the effects of learning on behavioural performance, we compared trials performed during the learning start period (n = 194–203 depending on the condition) with trials performed during the learning end period (n = 171–180 depending on the condition) in Monkey M. A similar learning course was observed, but not recorded, in the other two monkeys. To identify the effects of MPTP treatment, we compared, for each experimental condition, normal-state trials (n = 114–130 in Monkey M, n = 83–93 in Monkey R and n = 87–90 in Monkey G) with preS-stage trials (n = 130–134 in Monkey M, n = 88–100 in Monkey R and n = 95–101 in Monkey G). Errors in hand selection included errors made with either hand, while the other parameters (RT, MT, trajectories and kinematics) concerned only one hand. For the latter, we chose in each monkey the hand that showed, in the normal state, the more widely differentiated trajectories between the different conditions.

As the same animals were used throughout the experiments, we tested the significance of variations separately for the different monkeys. We used Student's t test to estimate the significance of differences between average RT, MT and initial slopes, and the χ^2 test (df = 1) to estimate the significance of differences between error frequencies. We considered three levels of significance: $P<0.05$, $P<0.01$ and $P<0.001$.

Histology

At the end of the experiments, the monkeys were fully anaesthetized and then transcardially perfused with saline followed by fixative solution. Brains were removed, sectioned in the frontal plane, and stained for tyrosine hydroxylase by immunohistochemistry. Mesencephalic tyrosine hydroxylase-positive cells were counted in regularly spaced sections that were equivalent for the different monkeys, and the total number was estimated after correction by the Abercrombie method. The percentage of neuronal loss in the substantia nigra pars compacta (A9) was evaluated by comparison with control values obtained in three intact monkeys. For details of histological methods, see François and colleagues (1999).

Results

The presymptomatic stage

The most sensitive data for the detection of motor symptoms were the measures of spontaneous activity. The different situations (home cage or experimental chair) and the different variables (total amount of activity or duration of active periods) gave similar results. The injection that produced a significant reduction of spontaneous activity (indicating akinesia) was considered as a limit separating the preS and symptomatic stages. For example, the proportion of active behaviour in the chair (mainly grooming) for the normal/preS/symptomatic stages was 29.0/37.2/7.8%, respectively, in Monkey M, 45.9/54.6/0% in Monkey R and 18.8/14.4/0% in Monkey G. The results presented in the following sections concern only the preS stage, in which the three monkeys were clinically normal: neither tremor, rigidity nor abnormal posture was detected, and the measures of spontaneous activity were normal. To reach this preS stage, we used a cumulative dose of 0.6 mg/kg (two injections) for Monkey M, 1.2 mg/kg (three injections) for Monkey R and 0.8 mg/kg (two injections) for Monkey G.

In the symptomatic stage, all three monkeys displayed postural difficulties that prevented them performing the task. In addition we observed mild transient rigidity and tremor in Monkeys R and G. In Monkey M, which was killed at this stage, the neuronal loss in A9 was 43% in comparison with normal monkeys. Thus, the preS stage analysed in Monkey M corresponded to a neuronal loss of <43%. The other two monkeys received two more MPTP injections, resulting in a severe parkinsonian state with stable akinesia, rigidity and tremor, and this was associated with a neuronal loss ofM 82–88%.

Reaction and movement times

At the beginning of the learning period in Monkey M, RTs were longer when obstacles were present. With training, RTs decreased and became similar for the different conditions. Such a pattern was reproduced in all monkeys in the normal state after training (Fig. 2, top). The MPTP treatment tended to reverse these learning effects: RTs increased mainly for the obstacle conditions. Within the RT, we distinguished between

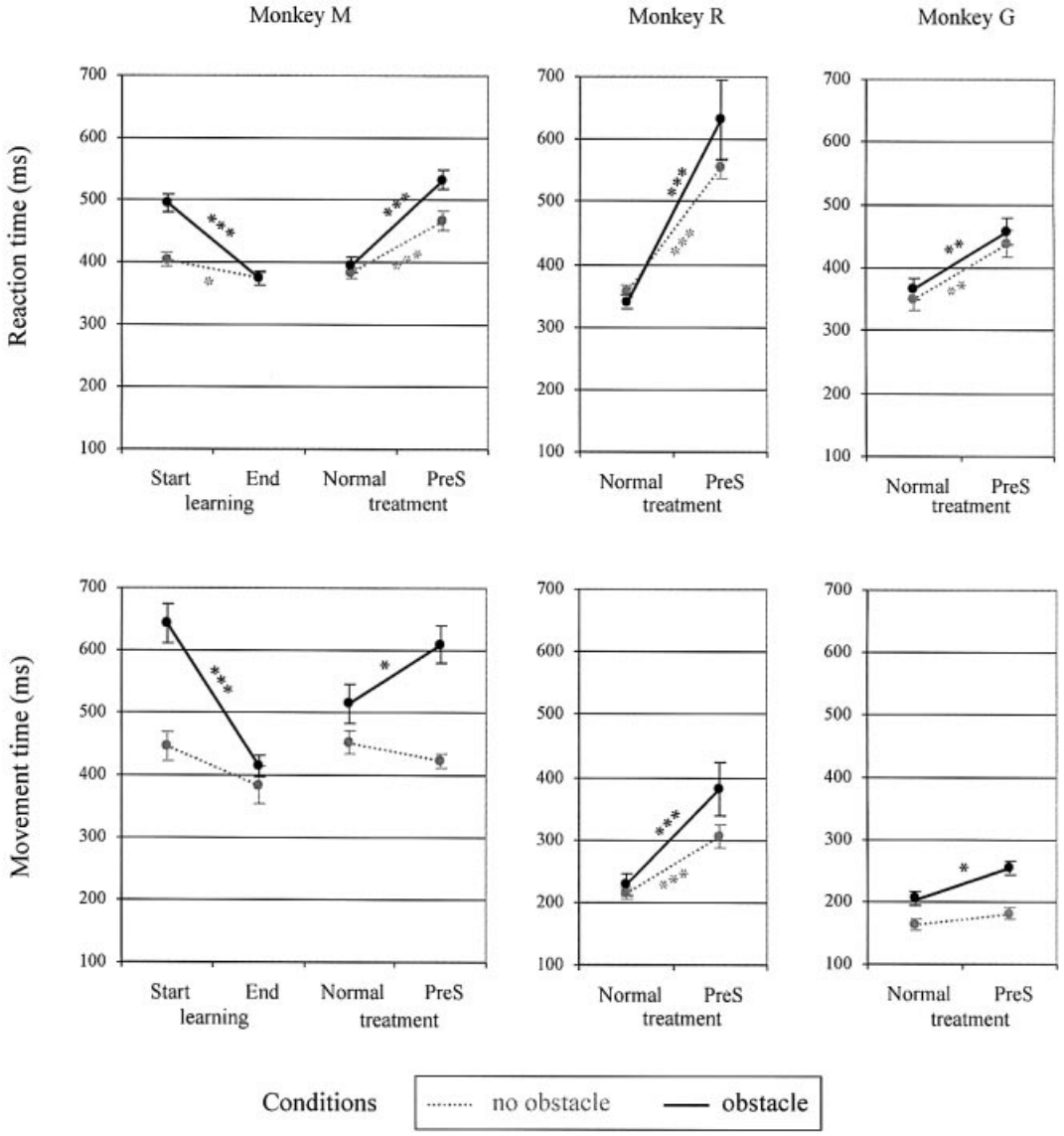

Fig. 2 Comparison of reaction time (*top*) and movement time (*bottom*) between learning start and end (Monkey M), and between normal and preS stages (three monkeys). The two obstacle conditions were grouped because they produced similar results. Error bars show the inter-block standard error of the mean. Student's *t* test was used to compare the means between the different stages. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

pre-EMG time (from reward appearance to biceps activation) and post-EMG time (from biceps activation to key release). In Monkey R the increase in RT was due to the increase in both pre-EMG and post-EMG times, whereas in Monkey G the increase in RT was entirely due to the increase in pre-EMG time (Fig. 3). EMG activations were not recorded in Monkey M.

In Monkey M, learning produced a decrease in MT, which was significant only for the obstacle conditions. Again, the MPTP treatment tended to reverse the learning effects: MTs increased mainly for the obstacle conditions (Fig. 2, bottom). In all three monkeys the relative increase in MT was inferior to the relative increase in RT: 10.7 and 30.7%, respectively, in Monkey M, 58.2 and 76.8% in Monkey R, and 12.7 and 24.1% in Monkey G. From this comparison, Monkey R, which received the highest dose of MPTP, appeared to be more impaired than the other two monkeys.

Hand selection

At the beginning of learning, the monkeys were already familiar with the task in the no-obstacle condition, and did not make any errors in hand selection. They made a few errors in the obstacle conditions when they were introduced (with a frequency of 7.1% in Monkey M). By the end of learning, the error frequency was <2% in all monkeys (Fig. 4). After MPTP treatment, all monkeys exhibited an increase in error

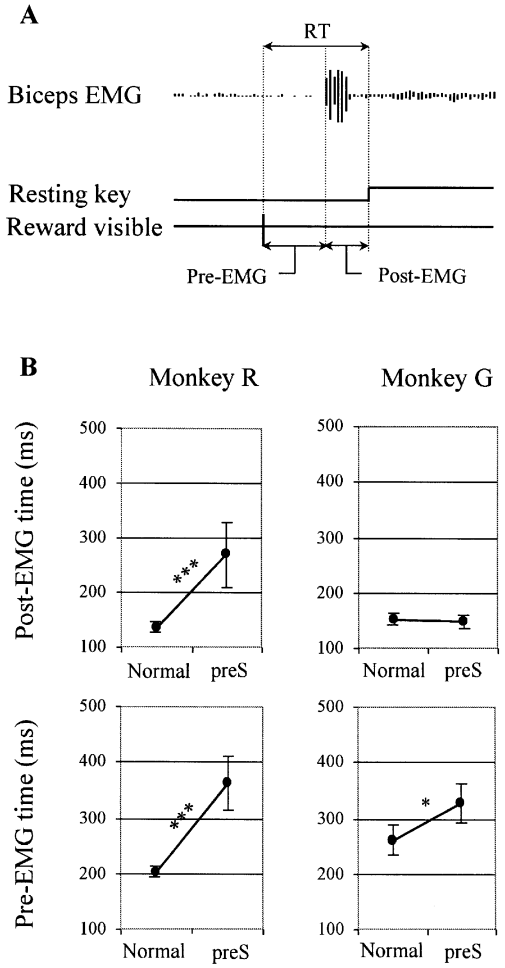

Fig. 3 Characterization of the RT increase due to MPTP treatment. (**A**) Separation of pre- and post-EMG reaction times based on the first biceps EMG activation. Pre-EMG time comprises the time between reward appearance in box and biceps activation; post-EMG time comprises the time between the biceps activation and the key release. (**B**) Comparison of pre- and post-EMG reaction times between normal and MPTP states (Monkeys R and G). Data are from the two obstacle conditions. Error bars show the standard error of the mean. Student's *t* test was used to compare the average pre- and post-EMG times between the normal and preS stages. $*P < 0.05$; $***P < 0.001$. Data were not available for Monkey M, which was not implanted with EMG electrodes.

frequency, which was significant only for the obstacle conditions (up to 6.1–7.9%, depending on the monkey).

Every monkey made errors with both hands, selecting the right hand instead of the left or vice versa. For the obstacle conditions in the preS stage, the frequencies of errors made with the right and left hand were 9.4 and 3.7%, respectively, in Monkey M, 3.7 and 8.5% in Monkey R, and 7.1 and 8.8% in Monkey G. The distribution of error frequency throughout the experimental schedule is shown in Fig. 8. Taken together, the results for the three monkeys show that the frequency of errors increased with the number of trials within a block and with the number of sessions within a day. A peak of error frequency was observed on the third day after the preceding MPTP injection (up to 12.8% on average).

Reaching trajectories

When first confronted with the obstacles, the monkeys produced both adapted trajectories (with initial slope anticipating the detour) and non-adapted trajectories (with initial slope directed towards the obstacle). Non-adapted trajectories led to either on-line correction or obstacle hit. With learning, obstacle hits disappeared, on-line corrections grew rare, and the variability of adapted trajectories decreased (Fig. 5A). As a result, the variability of initial slopes decreased for each condition (Fig. 5B). After a 9-day training period (~800 trials per condition), initial slopes showed good differentiation between conditions, as the mean for each obstacle condition differed from the mean for the no-obstacle condition with a significance level of $P < 0.001$. A similar pattern was obtained in the other two monkeys (Fig. 6, top), with a similar training duration.

MPTP treatment produced an increase in variability, which was significant for the three conditions in Monkey M, both the obstacle conditions in Monkey R, and only the basal-obstacle condition in Monkey G. This increase in variability was due both to greater variability among adapted trajectories and to a higher proportion of non-adapted trajectories (Fig. 6, bottom). For any given condition, we found examples of a trajectory with an initial slope that was more adapted to each of the other two conditions.

For both the obstacle conditions, trajectories were classified as adapted or non-adapted after a statistical analysis of their initial slopes (see Methods). Then, among non-adapted trajectories, we distinguished between those that were corrected to avoid the obstacle and those that hit the obstacle. The relative proportions of the different types of trajectories in the normal and preS stages are shown in Fig. 7, excluding all the trajectories that did not fit any statistical criterion (396 out of 1017, pooled data). In Monkey M the proportion of non-adapted trajectories decreased with learning from 62.9 to 7.0% ($P < 0.001$). The MPTP treatment tended to reverse this learning effect: the proportion of non-adapted trajectories increased from 0–4.2 to 37.0–64.7% ($P < 0.001$), depending on the monkey. The proportion of obstacle hits remained low (4.4–6.0%, depending on the monkey). Thus, most of the non-adapted trajectories were corrected before reaching the obstacle. Monkey R, which was considered as the most impaired on the basis of the increase in RT and MT, also exhibited the greatest increase in the proportion of non-adapted trajectories.

The distribution of the frequency of non-adapted trajectories throughout the experimental schedule is shown in Fig. 8. The general trend was for non-adapted trajectories to occur more frequently in the intermediate trials within a given block. Furthermore, the three monkeys tended to produce more non-adapted trajectories in a given obstacle condition when the preceding condition was the other

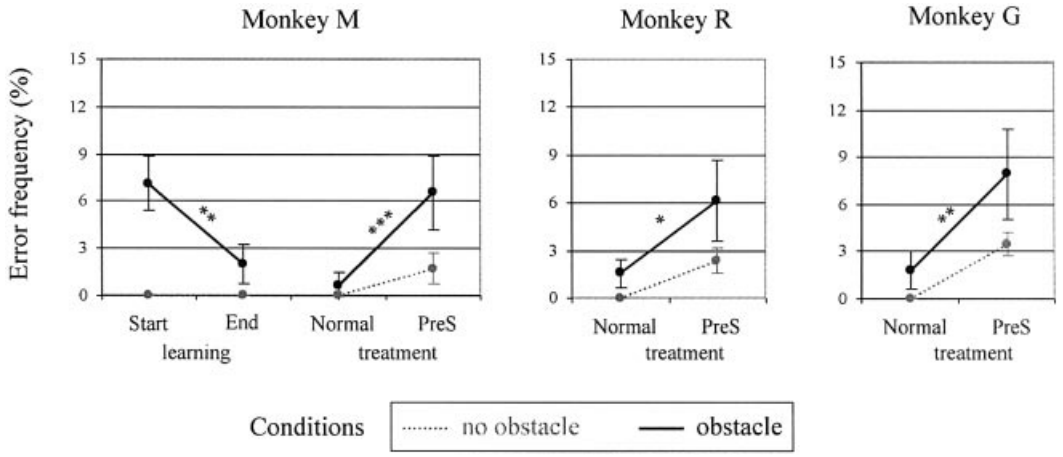

Fig. 4 Comparison of the frequency of errors in hand selection between learning start and end (Monkey M), and between the normal and preS stages (three monkeys). The two obstacle conditions were grouped because they produced similar results. Frequency refers to the number of errors per 100 trials. Error bars show the inter-block standard error of the mean. The χ^2 test was used to compare the frequencies between the different stages. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

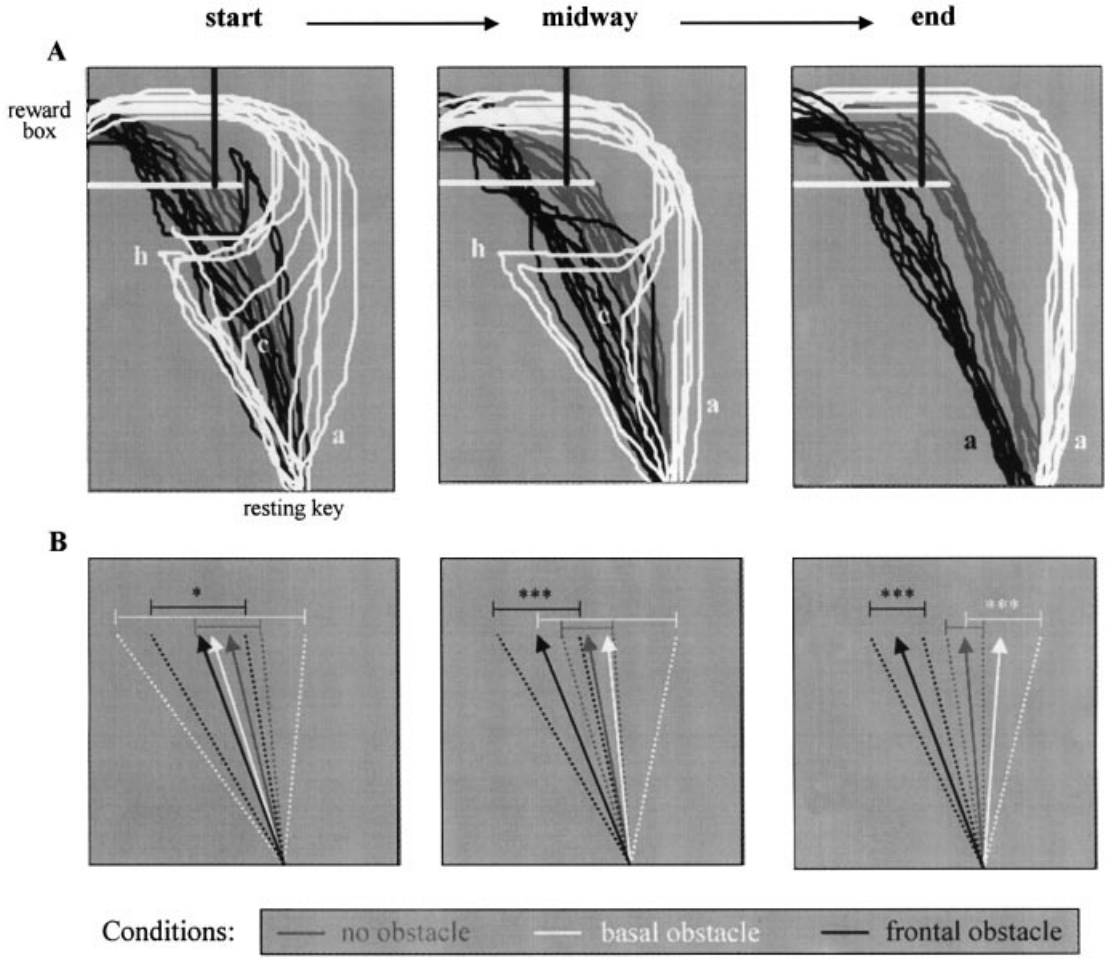

Fig. 5 Evolution of reaching movements during task learning (in Monkey M). (**A**) Examples of trajectories collected in one session (10 movements per condition). Straight lines indicate the position of the two obstacles when present. In the middle diagram, three types of trajectories are labelled: (a) trajectories with adapted initial slope; (c) trajectories including on-line correction; and (h) trajectories leading to obstacle hit. (**B**) Initial directions of all trajectories collected at each stage. Arrows represent the mean and error bars represent the standard deviation. Student's *t* test was used to compare the mean of each obstacle condition with the no-obstacle condition. $*P < 0.05$; $***P < 0.001$.

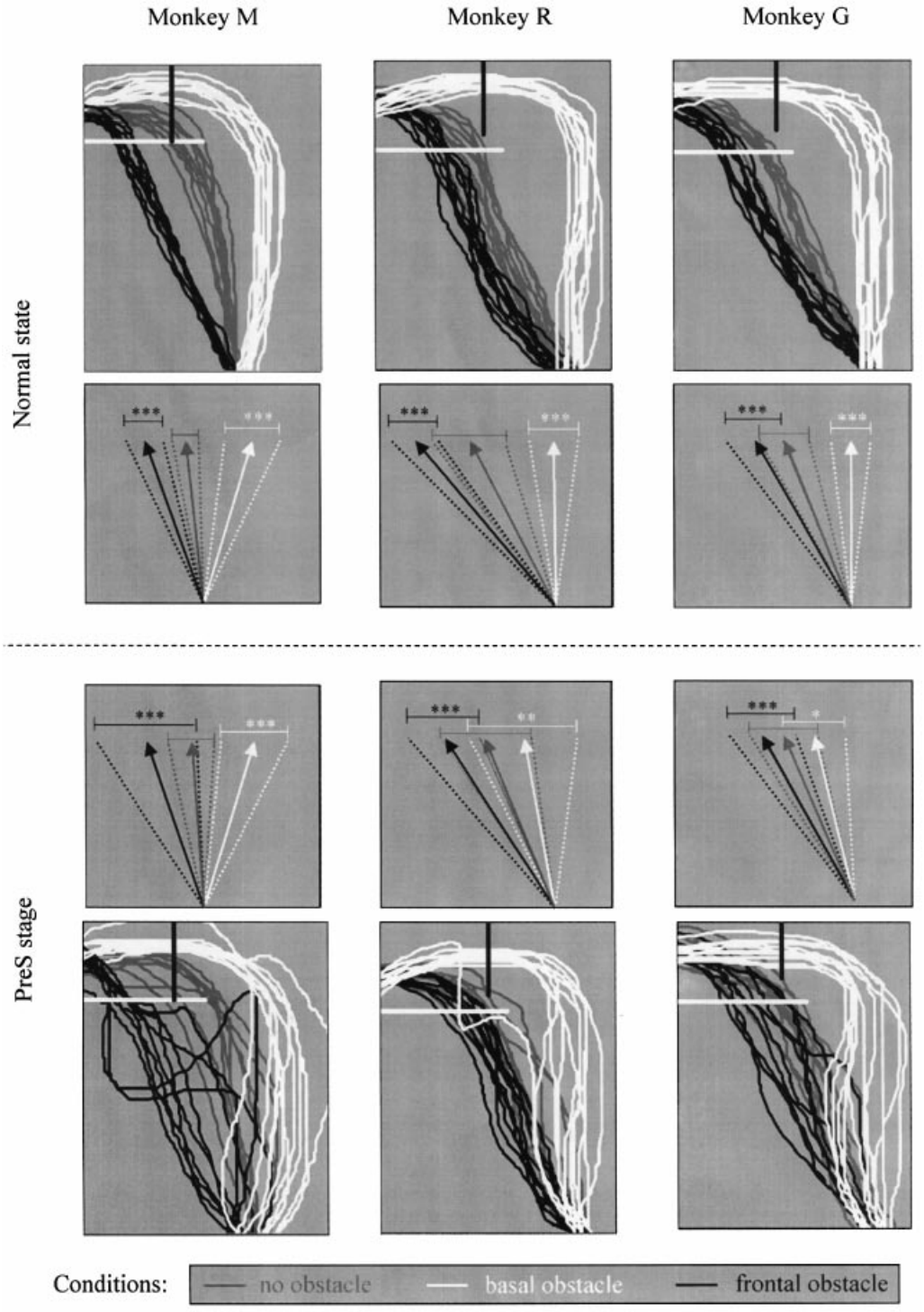

Fig. 6 Comparison of reaching movements between the normal and preS stages (three monkeys). For each stage the figure shows the trajectories collected in one typical session (10 trajectories per condition) and the initial directions of all trajectories collected in that stage. Arrows represent the mean and error bars represent the standard deviation. Student's *t* test was used to compare the mean of each obstacle condition with the no-obstacle condition. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

obstacle condition than when it was the no-obstacle condition: 29.8–36.1 and 13.3–24.3%, respectively, depending on the monkey. We found no effect of the number of sessions within a day. A peak of error frequency was observed on the third day after the preceding MPTP injection (up to 42.9% on average).

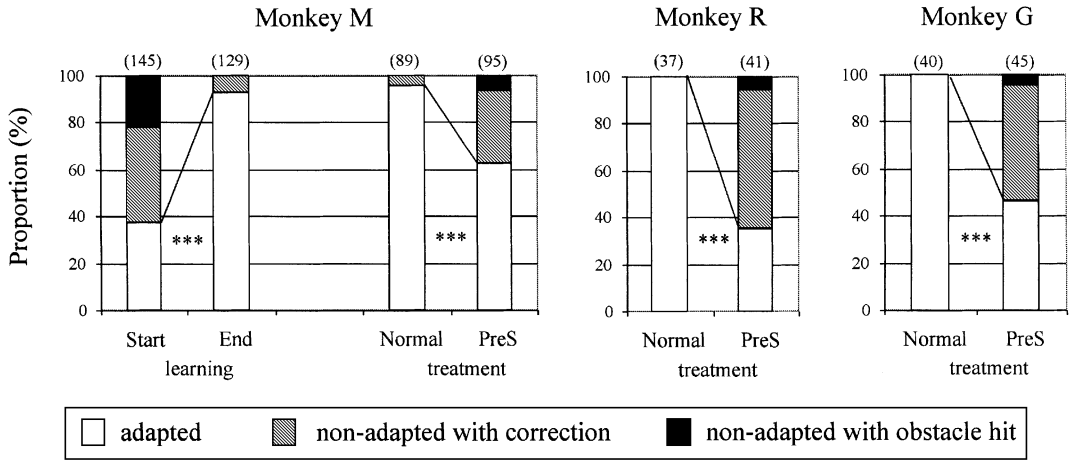

Fig. 7 Comparison of proportion of different types of trajectories between learning start and end (Monkey M) and between the normal and preS stages (three monkeys). Only classified trials (621 out of 1017, pooled data) are taken into account. The total number of classified trials is indicated above each diagram. Proportions are expressed as the number of trials of each type per 100 trials (%). The χ^2 test was used to compare frequencies between the different stages. ***$P < 0.001$.

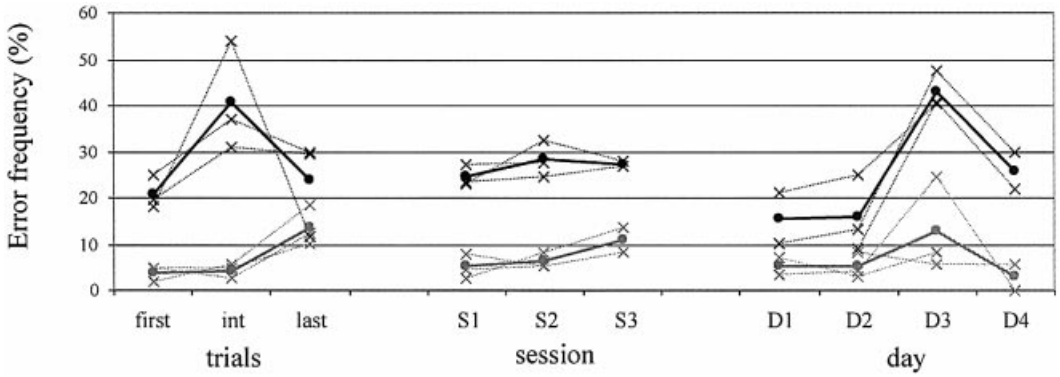

Fig. 8 Distribution of errors in hand selection (grey) and trajectory selection (black) throughout the preS stage (three monkeys). Data were collected in the two obstacle conditions, but concerned both hands for hand selection (n = 45 errors per 657 trials in all monkeys) and only one hand for trajectory selection (n = 88 errors per 332 trials in all monkeys). Frequency refers to the number of errors per 100 trials. Crosses indicate individual frequencies and circles indicate pooled data for all three monkeys. Different moments of the experimental schedule were considered (Fig. 1): blocks were divided into first, intermediate and last trials; days were divided into two or three experimental sessions (S1–S3) of six blocks, and the preS stage was divided into 3 or 4 days (from D1 to D4), D0 being the day of the preceding MPTP injection.

Kinematics of hand and eye movements

In the normal state the arm movement typically reached peak velocity just before entering the box. This movement was preceded by an ocular movement (i.e. a saccade) directed towards the reward, but there were no saccades performed during the execution (Fig. 9, left). In the preS stage we frequently observed what we called a 'split movement'. This was a movement divided into two or three submovements, corresponding to two or three velocity peaks or, in other words, two or three acceleration–deceleration cycles. This kinematic pattern indicates that reaching was restarted after a failed initial component. Split movements were frequently accompanied by saccades directed towards the hand or towards the obstacle, and occurred approximately between successive submovements. A typical example of such a gaze-assisted split movement is shown on the right of Fig. 9.

Results of quantification based on kinematic analysis (see Methods) are shown in Fig. 10. Split movements as well as saccade-containing trials were rare in the normal state (<5% in each monkey). For the obstacle conditions, MPTP treatment produced a significant increase in the frequency of split movements (up to 25.0–33.3% depending on the monkey) and saccade-containing trials (up to 18.1–36.4% depending on the monkey). For the no-obstacle condition, these frequency increases were weaker or absent. Of the split movements, a high proportion (61–82%) were accompanied by at least one saccade. Monkey R, which exhibited the greatest proportion of non-adapted trajectories, exhibited

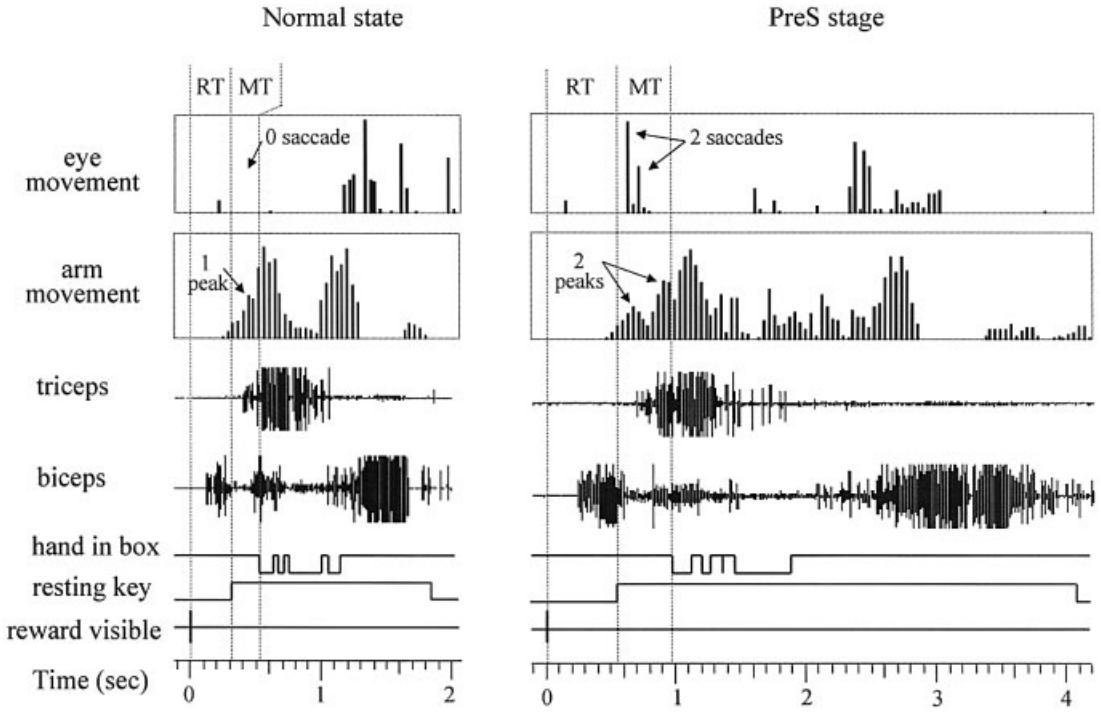

Fig. 9 Examples of the kinematics of a normal-state trial (left) and a preS-stage trial (right) with gaze-assisted split movement. (*Bottom*) Event markers used to determine the reaction time (RT) and the movement time (MT). (*Middle*) Electrophysiological recordings of biceps and triceps. Note that every burst of activity is delayed in the preS stage. (*Top*) Kinematics of eye and hand movements (arbitrary units). In both states the eye recording displays a saccade within the reaction time, corresponding to reward fixation. In the normal state, the movement time includes one velocity peak for hand movement, and no eye movement. In the preS stage, the movement time includes two velocity peaks for hand movement, and two saccades, the first one directed towards the moving hand and the second one back to the reward.

more gaze-assisted split movements (27.4%) than Monkey M (15.3%). Due to technical problems, ocular movements could not be recorded in Monkey G.

Impact of movement selection on RT, MT and kinematics

Concerning the relationships between initial slopes and kinematic parameters (Table 1), the following points emerge: (i) the contribution of non-adapted trajectories to the relative increase in RT due to MPTP treatment (+66.2%) was more than twice that of adapted trajectories (+30.7%); (ii) the relative increase in MT due to MPTP treatment mainly concerned non-adapted trajectories (+62.3%), since the MTs of adapted trajectories were close to normal values (+7.2%); (iii) split movements were in most cases initiated by either a non-adapted (36.9%) or an unclassified trajectory (36.7%), and adapted trajectories rarely (5.2%) required any additional velocity peak or gaze assistance; (iv) as non-adapted trajectories led to gaze-assisted split movements in only 36.9% of cases and to obstacle hits in only 11.2% of cases, we deduce that they were frequently (51.9% of cases) corrected on-line without gaze assistance.

Discussion

Many studies have reported that RT and MT are delayed both in monkeys with MPTP-induced parkinsonian symptoms (Doudet *et al*., 1985; Schultz *et al*., 1989) and in humans with Parkinson's disease (Evarts *et al*., 1981; Pullman *et al*., 1988). The present study shows that, at a preS stage of MPTP-induced parkinsonism in monkeys, RT prolongation is due mainly to a deficit in the selection of context-adapted movements, and MT prolongation is due mainly to the corrections required by ill-selected movements.

Impaired mechanisms of movement selection

In addition to a severe deficit in selecting the appropriate trajectory (with initial slope adapted to the condition), we found a mild deficit in selecting the appropriate hand (i.e. the hand ipsilateral to the baited box). With regard to the process of hand selection, errors rapidly became rare with training, reflecting the building of a strong association between the contextual cue (which box is baited) and the appropriate habit (which hand to move). The increase in frequency of wrong hand selection indicated that the C–H association was weakened by MPTP treatment. This deficit cannot be attributed to the preferential disabling of one particular

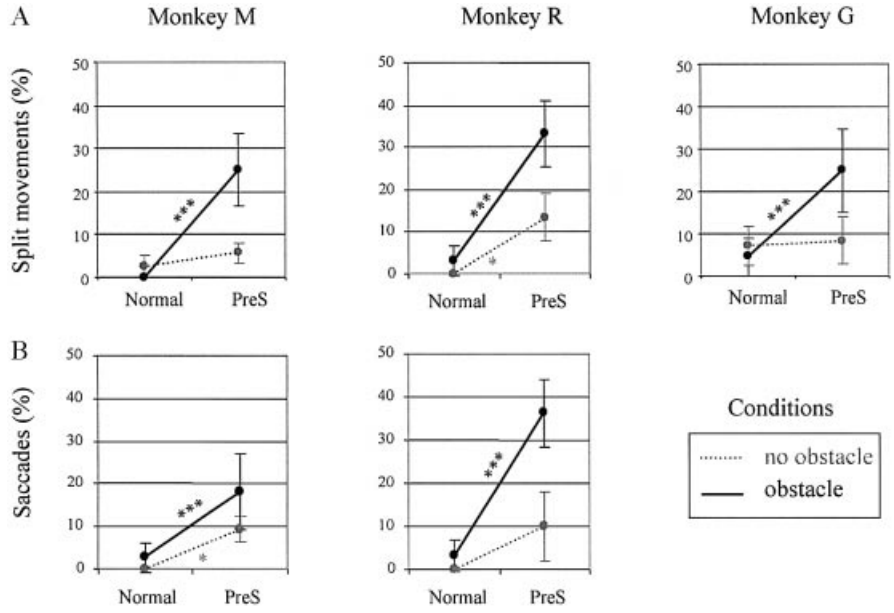

Fig. 10 Kinematics of eye and hand movements. (**A**) Comparison of the frequency of split movements (with at least two velocity peaks within the movement time) between normal and preS stages. Frequency refers to the number of trials with split movements per 100 trials. (**B**) Comparison of the frequency of saccade-containing trials (with at least one saccade during the movement time) between the normal preS stages. For technical reasons it was not possible to record eye movements in Monkey G. Frequency refers to the number of saccade-containing trials per 100 trials. The two obstacle conditions were grouped because they produced similar results. Error bars show the inter-block standard error of the mean. The χ^2 test was used to compare frequencies between the two stages. $*P < 0.05$; $***P < 0.001$.

hand, since all monkeys made errors with both hands. With regard to the process of trajectory selection, non-adapted trajectories (with initial slope directed towards the obstacle) were almost eliminated and adapted trajectories (with initial slope anticipating the detour) were stabilized after ~2 weeks of training. This suggests that the monkeys had spontaneously built strong associations between contextual cues (presence and position of obstacles) and the appropriate response (initial slope adapted to the condition). After MPTP treatment, the monkeys still produced some adapted trajectories, suggesting that they were still able to recognize the different contexts. However, the C–H associations were weakened, since non-adapted trajectories reappeared approximately as frequently as adapted trajectories.

Non-adapted trajectories might be due either to the activation of a wrong association between learned contexts and habits, or to the activation of a different behavioural strategy ignoring learned C–H associations. In support of the first alternative, we observed trajectories in the no-obstacle condition initiated as if a detour was required. In support of the second alternative, initial slopes of adapted trajectories resembled those produced during the first days of learning, with a high level of variability covering the whole range of possible directions. Whatever the case, the monkeys were unable to recall the learned C–H associations. This impairment cannot be explained in terms of deficits in processes such as direction coding, movement initiation, inhibition of direct movement, or adaptation to condition switching. A mere deficit in direction coding cannot explain errors in hand selection. A deficit in movement initiation is not supposed to increase the variability of the initial slopes. A deficit in inhibiting the direct movement would have led to shorter RTs for non-adapted (direct) initial slopes, but RTs were shorter for adapted (detouring) initial slopes. With a pure deficit in adaptation to condition switching, non-adapted trajectories would have occurred at the first trials of each block, but they were more frequently observed in the intermediate trials.

The prolongation of RT due to MPTP treatment appeared to result from the deficit in selecting adapted trajectories. Indeed, the RT increase for non-adapted trajectories was more than twice that of adapted trajectories. Furthermore, even in the case of adapted trajectories, a delayed RT may have resulted from a slowing in the mechanism of selection. Moreover, the greatest proportion of non-adapted trajectories was observed in the monkey (Monkey R) that exhibited the longest RT. In Monkey R, the RT prolongation corresponded to an increase in both pre-EMG (before biceps activation) and post-EMG (from biceps activation to movement onset) times.

Table 1 *Effect of initial slope on kinematic parameters of hand movement in the preS stage (three monkeys)*

Initial slope	*n* (trajectories)				RT increase (%)				MT increase (%)				Split movement (%)			
	M	R	G	Total	M	R	G	Total	M	R	G	Total	M	R	G	Total
Adapted	58	14	21	93	17.6	65.3*	9.3	30.7	1.3	12.0	8.3	7.2	10.2*	0.0	5.6	5.2
Non-adapted	37	27	24	88	34.9	109.9*	53.7*	66.2*	26.4	122.6*	37.9*	62.3*	24.2*	36.3*	50.3*	36.9*
Unclassified	42	55	54	151	41.6*	86.3*	21.1	49.7*	6.2	64.7	6.3	25.7	46.5*	40.4*	23.1	36.7*

Initial slopes were classified into three types (see Methods): adapted, non-adapted and unclassified. Unclassified trajectories did not fit any statistical criterion: their initial slope was intermediate between the adapted and non-adapted types. For each type of trajectory the following are shown: RT increase, MT increase and the frequency of split movements. RT and MT increases are expressed as percentages of normal state values. Frequency of split movements refers to the number of trials with split movements per 100 trials. These split movements, containing at least two velocity peaks, were gaze-assisted in most cases (61–82% depending on the monkey). *Values exceeding the 95% confidence interval of normal values.

However, in the less impaired Monkey G, the increase was restricted to pre-EMG times, corresponding to the time when movements were being selected.

Theoretical models built on the physiological literature (Berns and Sejnowski, 1996; Gurney *et al*., 2001) are useful at this point to understand the dysfunction of the processes of movement preparation. In these models, basal ganglia outputs (like the motor thalamus) are locally disinhibited by the direct striatopallidal pathway, whereas they receive widespread inhibition driven by the subthalamic nucleus via the globus pallidus. The specific disinhibited channel is thought to correspond to a specific selected action. Thus, a key point of the selection process is the focusing of activation within the striatum, which could be mediated by dopaminergic fibres. Indeed, the selectivity of pallidal responses both to passive limb manipulation (Filion *et al*., 1988) and to striatal stimulation (Tremblay *et al*., 1989) is decreased in monkeys with MPTP-induced dopamine depletion. Furthermore, dopaminergic axonal endings are suitably placed to modulate the efficiency of corticostriatal transmission, as they contact the neck of dendritic spines, the heads of which are contacted by cortical axons (Smith and Bolam, 1990). Dopamine release at these synaptic sites can produce short-term effects such as the filtration of cortical inputs: the strongest are allowed to pass whereas all the weaker ones are suppressed (Brown and Arbuthnott, 1983; Toan and Schultz, 1985; Garcia-Munoz *et al*., 1991). Dopamine receptors have also been reported to mediate long-term effects, such as synaptic plasticity (Wickens *et al*., 1996; Calabresi *et al*., 2000) and gene expression (Gerfen *et al*., 1990; Liste *et al*., 1995), which could play a role in reinforcement learning. In addition, the striatum is known to receive phasic and widespread waves of dopamine in response to the first signal that predicts a coming reward, or to the reward itself if unexpected (Schultz, 1986; Schultz *et al*., 1993).

Thus, in the context of our study, the appearance of the reward in the box is likely to have elicited a sudden release of dopamine within the striatum while the monkey was preparing a reaching movement. The dopamine could have exerted a short-term focusing of corticostriatal transmission that facilitated the selection of an adapted movement, and a long-term reinforcement of active corticostriatal synapses that facilitated subsequent appropriate selections. These mechanisms could explain why dopaminergic denervation induced errors in movement selection and why the monkeys were unable to relearn the C–H associations despite a 3-day training session (88–101 trials for each condition).

Preserved mechanisms of movement correction

MT prolongation appeared to be linked to RT prolongation and consequently to the impairment of movement selection. Indeed, the greatest MT prolongation was observed in Monkey R, which exhibited the longest RT and the greatest proportion of non-adapted trajectories. Moreover, the MTs of adapted trajectories were almost normal (with an increase of 7%), whereas the MTs of non-adapted trajectories were consistently delayed (with an increase of 62%). This differential effect of MPTP intoxication argues against mere bradykinesia and suggests that MT prolongation was due to the necessity to correct trajectories starting with a non-adapted initial slope. The monkeys retained the capacity to correct ill-selected trajectories since they rarely hit the obstacles (11% of non-adapted trajectories) and were in any case able to retrieve the reward. On the basis of kinematics, we identified two kinds of correction: on-line corrections (which did not split the velocity peak), representing 52% of non-adapted trajectories, and restart corrections (with at least two velocity peaks), representing 37% of non-adapted trajectories.

On-line corrections refer to a non-adapted initial slope combined with smooth trajectory, smooth kinematics and the absence of ocular movement. This kind of correction resembles that observed in the target shift paradigm, where a shift in target location occurs near the onset time of a reaching movement (Soechting and Lacquaniti, 1983; Goodale *et al*., 1986; Prablanc and Martin, 1992). To reach the final target, healthy human subjects produced fast automatic on-line corrections, even if they could not see their hand (in darkness) and if they could not consciously perceive the target jump (occurring during the saccade). As this kind of correction does not rely on visual feedback, it

must rely on one of two non-exclusive mechanisms: feedforward control based on the motor command, or feedback control based on proprioceptive inputs. A feedforward control could be sufficient, since deafferented patients perform as accurately as normal subjects in the target shift paradigm without vision of the hand (Bard *et al*., 1999). Two brain structures could participate in the network responsible for on-line corrections: the cerebellum, since patients with cerebellar ataxia are less likely to make a corrected reach after a target shift (Bonnefoi-Kyriacou *et al*., 1998), and the posterior parietal cortex, since contralateral corrective responses to a target shift are eliminated when transcranial magnetic stimulation is applied to this area (Desmurget *et al*., 1999).

Restart corrections refer to split kinematics, usually combined with ocular movements (in 72% of cases). When a monkey initiated its reaching movement, its gaze was directed towards the reward and it could not see its hands grasping the resting keys. Saccades were unlikely to be due to distractibility because they rarely occurred in the no-obstacle condition or if the initial slope was correctly selected. Thus, the saccades appeared to assist the achievement of an ill-selected movement by providing visual feedback from the hand and/or obstacle. The need for visual feedback again suggests the involvement of the cerebellum, since patients with cerebellar dysfunction have more difficulty in producing visually guided than self-generated movements (Beppu *et al*., 1987; van Donkelaar and Lee, 1994). However, the differential contribution of the basal ganglia and the cerebellum in internally generated versus externally guided reaching movements remains a controversial issue. While partial dissociation was found between the dentate and pallidal neurons (Mushiake and Strick, 1993, 1995), inactivation of the globus pallidus internalis (GPi) produced similar disabling of limb movements whether or not there was an external cue (Mink and Thach, 1991; Inase *et al*., 1996). In our view, consistent with these apparently contrasting results, the cortico-striato-pallido-thalamic system could act as a filter in both types of movement. If there is a visual target, the cortico-cerebellar-thalamic system could assist movement achievement by reducing the discrepancy between target and hand positions given by sensory inputs (Glickstein and Stein, 1991). This view is corroborated by a PET study (Jueptner and Weiller, 1998) comparing tasks of line retracing versus new line generation: the basal ganglia were similarly activated in both tasks, whereas the cerebellum was specifically activated by the difference between tasks, which isolates processes that minimize error between pointer and target.

In our task, which was visually guided, learning was likely to have reduced the contribution of the cerebellum, as the repertoire of context-adapted movements was formed progressively. But with dopamine depletion the cortico-cerebellar-thalamic system could take charge of the necessary corrections after movement onset (once the time of selection is over), on the basis of either proprioceptive (on-line corrections) or visual (restart corrections) feedback.

The MPTP model and Parkinson's disease

Our results concerning the doses of MPTP and the nature of motor symptoms do not differ from current studies in the same species, which report a high level of variability in sensitivity between monkeys (Taylor *et al*., 1997). The frequency of selection disorders reached a peak on the third day (D3) following the last MPTP injection. D3 is thought to be posterior to the acute MPTP effects and anterior to the occurrence of behavioural recovery. The acute effects, as experienced by human drug addicts (euphoric state with hallucinations and jerking of the limbs), last only a few hours (Langston *et al*., 1983). In our monkeys, we observed that jerky movements had totally disappeared 45 min after the injection. Moreover, MPTP and its metabolites are completely eliminated after 3 days (Przedborski *et al*., 2001). Behavioural recovery usually develops after several days and can take from weeks to months, depending on the severity of the symptoms (Elsworth *et al*., 2000). We do not know if our monkeys would have fully recovered their ability to select movements, or if they would have relearned the task, because they received another MPTP injection to test the appearance of motor symptoms. The physiological mechanisms that lead to behavioural recovery are likely to be specific to non-human primates (Burns, 1991). Thus, we consider that the post-injection period extending from D2 to D4 is suitable for observing the effects of dopamine depletion. Indeed, the parkinsonian motor symptoms obtained after the next injection also reached a peak on D3.

Several authors have described a so-called 'frontal syndrome' in motor asymptomatic MPTP-treated monkeys (Slovin *et al*., 1999; Schneider and Kovelowski, 1990; Taylor *et al*., 1990), although dopamine depletion in the frontal cortex appeared to be minor in comparison with the striatum (Schneider, 1990). However, some frontal signs, such as lack of inhibition or perseverative responses, can also be interpreted as a frontostriatal dysfunction resulting in difficulty in building and recalling C–H associations. For example, Taylor *et al*. (1990) tested the capacity of MPTP-treated monkeys to learn a very complex object retrieval/detour task because the positions of the reward in the box, of the box entrance and of the box itself were modified trial after trial. Some frequent errors exhibited by MPTP-treated monkeys were barrier reaches (when they hit a closed side of the box) and awkward reaches (when they used the hand further from the open side). According to the authors, these errors resulted from failure to suppress the tendency to reach directly for the reward. Yet they could also indicate that the monkeys had difficulty in building associations between open side and adapted trajectory or between open side and appropriate hand; hence they required sensory feedback (contact with the barrier) to find the box entrance.

For obvious reasons the preS stage of Parkinson's disease is difficult to study in humans, and experiments on diagnosed patients are complicated by gross motor symptoms, compensatory mechanisms and drug therapy. Despite these limitations, several clinical studies have reported both deficits in learning C–H associations and a tendency to rely on external feedback. A classical study by Flowers (1976) showed that Parkinson's disease patients did not benefit from training, because they continued to use visually guided (feedback) movements instead of ballistic (feedforward) movements to track a target moving along a predictable path. Jackson *et al*. (1995) confirmed these seminal observations by showing that memory-guided (and not visually guided) prehension movements are impaired in Parkinson's disease, and that only the transport (not the grasp) component is affected. Furthermore, learning deficits concern not only motor but also cognitive habits, independently of frontal lobe dysfunction (Saint-Cyr *et al*., 1988; Knowlton *et al*., 1996). However, it remains problematic to dissociate a difficulty in building new habits from a difficulty in recalling old habits. And the hypothesis that Parkinson's disease begins with the loss of the ability to select personal habits adapted to everyday contexts has yet to be demonstrated.

Conclusions

Our results show that preS MPTP-treated monkeys conserved the movement repertoire built when they were intact but had difficulty in selecting the movement adapted to the context. This dysfunction of the mechanisms of selection could be due to a lack of dopamine-mediated focusing and strengthening of corticostriatal transmission. To correct ill-selected movements, preS MPTP-treated monkeys used either proprioceptive or visual feedback. These compensatory mechanisms are thought to recruit cerebral networks outside the circuits linking the cortex and basal ganglia. Impairment of procedural learning and reliance on external cues are well documented in the Parkinson's disease literature, but a specific deficit in selecting context-relevant habits has yet to be demonstrated. Although it appeared in preS monkeys, the impairment of selection mechanisms could be related to motor symptoms, since the difficulty in retrieving context-adapted habits may impede the initiation of action. In addition, the use of compensatory strategies may engage most of the attentional resources, preventing more than one action being performed at a time, and hence limiting the behavioural repertoire. In a more advanced stage of the disease, a lack of selection or the coselection of antagonist programmes would therefore result in akinesia and rigidity.

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