Disruption of information processing in the supplementary motor area of the MPTP-treated monkey
A clue to the pathophysiology of akinesia?

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Summary

It has been suggested that the underactivity of mesial frontal structures induced by dopamine depletion could constitute one of the main substrates underlying akinesia in Parkinson’s disease. Functional imaging and movement-related potential recordings indicate an implication of the frontal lobes in this pathological process, but the question has not yet been investigated at a cellular level using single unit recording. We therefore compared neuronal activity in both the presupplementary motor area (pre-SMA) and the supplementary motor area proper (SMAp) of the Macaca mulatta monkey during a delayed motor task, before and after MPTP treatment. In the pre-SMA, which receives strong inputs from the prefrontal cortex, the baseline firing frequency and the percentage of neurons responding to visual instruction cues decreased in lesioned monkeys. In the SMAp, which sends direct outputs to the primary motor cortex, not only was the response to visual cues impaired, but the percentage of SMAp neurons responding to intracortical microstimulation fell and the threshold of response rose. Neuronal activity after the Go signal diminished sharply in both structures in the symptomatic animal and the discharge pattern became more irregular; in the SMAp neuronal activity remained modified longer. Most of these changes could already be observed in the presymptomatic animal presenting no clinical signs of parkinsonism. These data would indicate that, at the moment when dopamine depletion has impaired the ability of cortical neurons to operate the focused selection of incoming information giving instructions for movement, pre-SMA and SMAp neurons are also in a state of severe hypoactivity. The conjunction of these phenomena could play a critical role in the genesis of akinesia.

Keywords: akinesia; monkey; MPTP; single unit activity; supplementary motor area

Abbreviations: CRT = cellular reaction time; fMRI = functional MRI; ICMS = intra-cortical microstimulation; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MT = movement time; PMT = mean premotor time; pre-SMA = presupplementary motor area; RT = reaction time; RTi = return time; RW = reward time; SMAp = supplementary motor area proper; TDM = total duration of the modification; TH = tyrosine hydroxylase

Introduction

The impairment of the spontaneous execution of movement constitutes the most evident and disabling characteristic of Parkinson’s disease. This disorder can manifest itself in different forms such as akinesia, bradykinesia and hypokinesia, symptoms which are frequently associated but can to some extent be separated (Berardelli et al., 2001). Akinesia has been defined as a delay or a failure in movement initiation (Hallett et al., 1991). Its pathophysiology has yet to be elucidated. A number of clinical studies have shown that Parkinson’s disease affects not only the execution of motor programs but also the control of stimulus analysis and response selection (Jahanshahi et al., 1992; Cooper et al., 1994; Chen et al., 2001). This indicates that there may be a disruption of the different stages of information processing in Parkinson’s disease. It has already been suggested that the basal ganglia may play an important role in the control of cortical activity by providing an internal cue that regulates movement planning (Brotchie et al., 1991; Cunnington et al.,...
Functional imaging studies carried out on parkinsonian patients have revealed that the metabolism of several areas of the frontal lobes is modified during the performance of a motor task (Eidelberg et al., 1990; Jenkins et al., 1992; Rascol et al., 1992, 1994, 1998; Playford et al., 1993; Jahanshahi et al., 1995; Samuel et al., 1997; Catalan et al., 1999; Sabatini et al., 2000; Haslinger et al., 2001). Most of these studies have shown, in particular, a hypoactivity of the mesial premotor and prefrontal areas in patients compared with healthy subjects (for review see Berardelli et al., 2001). It has consequently been suggested that an underactivity in these structures, attributable to the dopamine cell loss characteristic of Parkinson’s disease, may be the functional substrate underlying akinesia in this pathology (Haslinger et al., 2001). In this connection it is interesting to note that vascular or tumoral lesion of the mesial premotor area can produce akinetic symptoms not unlike those observed in Parkinson’s disease (Dick et al., 1986; Meador et al., 1986; Haussermann et al., 2001). An overactivation of lateral premotor areas has also been reported in Parkinson’s disease patients, generally interpreted as a compensation for deficits in the midline motor system during internally generated tasks (Cunnington et al., 1999; Berardelli et al., 2001). This type of study has provided extremely valuable descriptions of the metabolic changes that regulate the activity of the premotor cortices (Stephan et al., 1995; Deiber et al., 1996, 1999; Hikosaka et al., 1996; Juettner et al., 1997; Boecker et al., 1998; Petiti et al., 1998; Jenkins et al., 2000). Unfortunately, however, neither PET nor event-related functional MRI (fMRI) can deliver precise information on cortical activation at cellular level, such as time-linked data on the modification of firing rate or an exact evaluation of the activation of excitatory or inhibitory neuronal networks corresponding to the modifications observed in cerebral blood flow.

Electrophysiological techniques have also been used to investigate activity in midline cortical areas in Parkinson’s disease patients (for review see Berardelli et al., 2001). Early studies based on simple non-cued movements reported a frequent diminution of activity in the early part of the pre-movement EEG potential (Dick et al., 1989). Subsequent research showed that these abnormalities were particularly marked when Parkinson’s disease patients performed self-paced movements (Cunnington et al., 1995; Jahanshahi et al., 1995). It was therefore suggested that Parkinson’s disease patients were more reliant on external cues because they could not use predictive models (Cunnington et al., 1995). Other teams showed that the pre-movement potential of Parkinson’s disease patients also deteriorates when subjects have to choose between different types of movement (Touge et al., 1995; Praamstra et al., 1996; Dirnberger et al., 2000). Different techniques, such as event-related desynchronization, have revealed alterations in the pattern of EEG rhythms, which are attenuated prior to movement onset in Parkinson’s disease patients (Defebvre et al., 1996; Magnani et al., 1998). These techniques complement imaging studies in that they provide temporal information on cortical activation, but the data they furnish concern the global activation of a given cortical area and not the precise nature of the disruption observed in information processing.

A number of single unit activity studies have already been performed in monkeys rendered parkinsonian by the systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), as well as in parkinsonian patients, but the studies so far available have concentrated on the subcortical structures, such as the subthalamic nucleus (Wichmann and DeLong, 1996; Bergman et al., 1998; Magnin et al., 2000) and the internal pallidum (Filion et al., 1988; Filion and Tremblay, 1991; Beric et al., 1996; Boraud et al., 1996, 1998; Lozano et al., 1996). Their results have shown a complex hyperactivity in both these structures that could brake neuronal activity in the frontal mesial cortex by inhibiting the motor thalamus (Albin et al., 1989; DeLong, 1990; Wichmann and DeLong, 1996). The electrophysiological activity of the cortical regions in the parkinsonian situation has hardly been recorded, and there are few data on their role in the pathophysiology of Parkinson’s disease. Only two studies have been carried out so far, to our knowledge, on cortical areas in the MPTP-treated monkey. These showed a drastic impairment of neuronal activity in the primary motor cortex (Doudet et al., 1990; Watts and Mandir, 1992) and a prolongation of activity after movement onset in the supplementary motor area (SMA; Watts and Mandir, 1992).

The frontal mesial cortex, because of its connections with the basal ganglia (Schell and Strick, 1984; Dum and Strick, 1991; Matelli and Luppino, 1996; Sakai et al., 2000) and the major role it plays in motor planning (Tanji, 1994; Picard and Strick, 1996), occupies a key position in the premotor organizational chart. It can be divided into two distinct areas: the presupplementary motor area (pre-SMA) and the supplementary motor area proper (SMAp) (Luppino et al., 1991; Matsuzaka et al., 1992). Both these areas connect separately to other cortical and subcortical structures (Matelli and Luppino, 1996). The pre-SMA is thought to be involved in the selection and updating of motor programs (Shima et al., 1996) and in the learning and control of sequential behaviour (Clower and Alexander, 1998; Nakamura et al., 1998; Shima and Tanji, 2000), whilst the SMAp, which receives somatosensory inputs and is somatotopically organized (Luppino et al., 1991), would seem to have a more executive function in motor control (Picard and Strick, 1996; Picard and Strick, 2001). What is certain is that both these areas are under the influence of the dopaminergic system, either directly through the meso-cortical network (Thierry et al., 1973; Le Moal and Simon, 1991; Williams and Goldman-Rakic, 1993) or indirectly via the cortico-subcortical loops (Alexander and Crutcher, 1990; Schultz, 1998).

To determine what modifications parkinsonism induces in the frontal mesial cortex and which aspects of neuronal
processing are affected, we recorded unit activity in the pre-SMA and the SMAp before and after MPTP intoxication in the monkey. Two monkeys were trained to perform a delayed motor task in which they had to action a joystick on the basis of prior visual information, a paradigm which allowed evaluation of the role played by these areas both in the analysis of information necessary for the construction of a motor program and in the initiation of the correct behavioural response. To mimic the progressive evolution of human Parkinson’s disease, a very gradual schedule of MPTP intoxication was used. This allowed us to compare data for three situations: before-MPTP, presymptomatic and symptomatic.

Material and methods

Monkeys and paradigm

Experiments were carried out in two female monkeys (Macaca mulatta) weighing 5 and 6 kg, housed in individual primate cages. Their care was supervised by veterinarians skilled in the maintenance of non-human primates, in strict accordance with the European Community Council Directive for experimental procedures in animals. Monkeys were trained to perform a delayed motor task in which they had to push or pull a 7-cm high joystick according to prior visual instructions (Fig. 1).

Seated in a primate chair with their heads immobilized facing a video monitor (distance 20 cm) and their left hands restrained, monkeys were trained to keep their right hands on the joystick until the Go signal appeared. The trial was interrupted if the monkey took its hand off before the Go signal. After 3 s (reference period), an onset cue (6 cm in diameter) appeared in the centre of the screen for 500 ms. One to 3 s after extinction of this cue, a white target (3 × 3 cm) appeared either at the top or the bottom of the screen (distance 10 cm). If it appeared at the top, the monkey had to push the joystick after the Go signal; if it appeared at the bottom, it had to pull. There was a variable delay (1–3 s) between target presentation and the appearance of the Go signal (a green cue in the centre of the screen), after which the monkey had 3 s to perform the correct movement in order to get the reward (0.5 ml of fruit juice). Movement onset was determined by an infra-red beam and movement end by a contact-maker (amplitude 45°). We studied the following kinematic parameters: (i) behavioural reaction time (RT), i.e. the interval between the Go signal and the onset of movement; (ii) movement time (MT), corresponding to the duration of the first component of movement (push or pull); (iii) reward time (RW), i.e. the period during which the monkey received the reward; both monkeys took the habit of keeping the joystick in the pushed or pulled position during this period, which was of variable duration; (iv) return time to initial position (RTi), i.e. the time needed for the joystick to return to the neutral position. A spring device helped pull the lever back, so that the monkey had little effort to make.

Surgery

After completion of the training period (3 months), a stainless steel recording chamber (diameter 19 mm; Narishige, Japan) was implanted onto the skull under general anaesthesia using ketamine (10 mg/kg; PanPharma, Fougères, France), xylazine (2 mg/kg; Sigma, Paris, France), diazepam (0.5 mg/kg; Roche, Neuilly, France) and atropine sulfate (0.2 mg/kg; Meram, Melun, France). Supplemental doses of ketamine and xylazine were given as necessary. The centre of the cylinder was stereotactically positioned at A24 and L0 in both monkeys. A head holder was embedded with dental cement (Omnium dentaire, Bordeaux, France) around the chamber in order to immobilize the head of the monkeys. Antibiotics (ampicillin, 100 mg/kg; SmithKline Beecham, Nanterre, France) and analgesics (prodafalgan, 30 mg/kg; UPSA, Agen, France) were administered for 1 week after surgery.

MPTP intoxication

After a 6-month pre-MPTP period, the two monkeys were treated three times a week with injections of MPTP hydrochloride (0.1 mg/kg, i.v.; Sigma, St Louis, MO, USA) in saline. Injections were performed in the evening after recording sessions (>18.00 h) under slight sedation with ketamine (10 mg/kg). Monkeys’ behaviour was clinically assessed every morning at 09.00 h. Two examiners independently rated animals’ levels of performance on a
parkinsonian monkey clinical rating scale (MCRS; Benazzouz et al., 1992) as they reached for appetising fruit or moved spontaneously. The two ratings were then averaged. The concordance of their observations was studied using Kendall’s correlation coefficient. The following symptoms were assessed: tremor (0–3); variation in the general level of activity (0–3); body posture (flexion of spine; 0–3); vocalization (0–2); freezing (0–2); rigidity of each arm (0–3 for each upper limb); and arm movements (reaching for food with each arm; 0–3 for each upper limb). Normality was classified 0, severe disorders 3. The maximum MCRS was 25. Intoxication was prolonged until monkeys reached a stable parkinsonian state (6 < MCRS < 10). This state was maintained by additional injections of MPTP if necessary. Neither of the monkeys required tube feeding at any stage. Neuronal activity was recorded throughout the procedure, which lasted approximately 9 months for each monkey. We were therefore able to compare three situations in the same animals: (i) before MPTP treatment; (ii) presymptomatic (MCRS ≤ 3); and (iii) symptomatic (MCRS > 3).

Neuronal recording
Recordings were made first before MPTP intoxication, then in the presymptomatic and symptomatic situations. Extracellular single-unit activity was recorded with tungsten microelectrodes (FHC; Bowdoiham, ME, USA) insulated with epoxy (impedance 1–1.5 MΩ at 1 kHz) inserted through the dura matter into the cortex, using a hydraulic micro-manipulator (Narishige Japan, MO-9B). The electrode was moved through the cortex in increments of 5–10 μm. Neuronal activity was amplified (10 000), filtered (300–3 kHz) and displayed on an oscilloscope. Spikes were selected from background activity with a window discriminator and then processed through an analogue–digital interface and stored online on a microcomputer. Neuronal response to neutral visual information and to reward were also tested randomly between trials. Approximately 50 trials were recorded for each neuron and each direction of movement (push and pull). Deep receptive fields were then studied by gently mobilizing the different joints of the contralateral upper and lower limbs.

Microstimulation
We performed intra-cortical microstimulation (ICMS) by applying a train of cathodal pulses (width 0.2 ms, train duration 50–150 ms at 300Hz) through a constant-current stimulator and the electrode used for extracellular recording. Movements were recorded only if they were repeatedly provoked and clearly identified by two observers. The threshold of effective current was sought systematically. This was usually under 50 μA in the SMAp and over 50 μA in the pre-SMA. Microstimulation was first performed to map both areas in the normal situation; this mapping was then checked in lesioned monkeys. The characterization of the motor response induced by ICMS in each region allowed us to localize a forelimb representation within each area. For quantitative analysis, we voluntarily limited our study to these areas.

Statistical analysis of unit activity
We only analysed data from neurons recorded in the arm regions of the pre-SMA and SMAp. Peri-event raster displays and histograms of neuronal activity were constructed by aligning neuronal activity to a specific event: onset cue, target presentation, onset of delay period, Go signal, onset of movement. Event-related modifications of activity were detected by comparing neuronal activity related with a specific event with activity during the reference period. Neuronal activity was studied for: 500 ms following the onset cue, 500 ms following target presentation, 1000–3000 ms during the delay period and 150–1250 ms after the Go signal (corresponding to the optimal period during which neuronal changes occurred). These time windows were determined from a sample of 50 movement-related neurons in each area. A change in neuronal frequency was considered significant if it deviated by ± 2 SD from mean activity during the reference period in at least two consecutive 50 ms bins.

For statistical analysis we used two parameters: (i) the relative modification of neuronal firing frequency, i.e. the ratio of the firing frequency recorded during a given period compared with the firing frequency recorded during the reference period; and (ii) the percentage of neurons presenting event-related changes at each stage of the task. The first parameter was used for the analysis of all recorded neurons whatever their response. This approach gave us a global index of neuronal activity within each area. A two-way analysis of variance (ANOVA) was performed for both areas (pre-SMA and SMAp) and for the three situations (pre-MPTP, presymptomatic, symptomatic). The dependent variable was the relative firing frequency calculated for all recorded neurons. For post hoc analysis we used a Fisher test with Bonferroni/Dun’s correction. Discharge frequency was not calculated for the delay period since neuronal activity was frequently inhibited during this period. The second parameter, i.e. the percentage of neurons presenting event-related changes, was used (i) for the analysis of neuronal activity during the Go trials in which animals responded correctly, and (ii) for analysis of the activity of the same neurons during the Go trials in which animals did not make the correct movement. For each parameter we used a χ² test to compare the data obtained in the three situations. Relative discharge frequency was not compared (in this second analysis), because the low level of correct response in symptomatic monkeys made it impossible to constitute a representative sample.

For those neurons presenting a modification of firing activity after the Go signal, we then calculated mean cellular reaction time (CRT), i.e. the period of latency between the Go signal and the modification of neuronal activity, mean pre-
motor time (PMT), i.e. the period between the modification of neuronal activity and movement onset (Fig. 1), and total duration of the modification (TDM), i.e. the length of the period following the Go signal during which neuronal activity remained modified.

**Histology**

At the end of the protocol, electrolytic lesions were made by applying an anodal direct current (20 μA, 20 s) with the recording microelectrode. One week later, monkeys were deeply anaesthetized (Nembutal, 100 mg/kg) and perfused through the ascending aorta with 500 ml of 0.9% saline, followed by 2 l of 4% paraformaldehyde in phosphate buffer (pH 7.4) as fixative. After the position of the recording chamber was marked on the surface of the brain, the brain was removed from the skull and sliced into 5 mm frontal sections for the mesencephalon and 20 mm frontal sections for the mesial frontal cortex. Mesencephalon sections were post-fixed for 12 h at 4°C in 20% sucrose in Tris-buffered saline (pH 7.4) and frozen in isopentane cooled on dry ice. Frontal lobe sections were then cut into 30 μm frontal sections with a cryostat. Dopamine depletion was measured using tyrosine hydroxylase (TH) immunohistochemistry (IR). Sections were incubated overnight at 4°C in serum containing TH antibody (anti-TH) (Biorad, Ivry/Seine, France) diluted 1 : 200 in PBS, mounted on gelatine-coated slides, dried, dehydrated in gradual concentrations of ethanol, cleared in xylene and coverslipped in Neoantelan (Polylabo, Strasbourg, France). The level of dopamine depletion was evaluated by counting the number of substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) neurons identified by tyrosine hydroxylase labelling. Serial coronal sections (50 μm) were stained with hemalun-chrome (Sigma). The coordinates of each recorded cell, coupled with marker lesions and electrode tracks, allowed us to situate precisely each recording site. The border between the pre-SMA and the SMAp was determined using microstimulation data, sulcal landmarks and cytoarchitectonic criteria.

**Results**

**Clinical data**

Presymptomatic MPTP-treated monkeys (MCRS = 0.49 ± 0.70) presented normal behaviour in their cages and no clinically observable rigidity. Only a very slight decrease in general activity was occasionally observed (Table 1). Their level of correct performance of the task was, however, globally lower than in the pre-MPTP situation (51% success rate versus 82%, P < 0.05). Non-movement was the most frequent type of incorrect response (Table 2). Although behavioural RT and RW were normal, the MT and RTi increased significantly.

Symptomatic MPTP monkeys (MCRS = 7.89 ± 1.90) presented moderate rigidity, reduced spontaneous locomotor activity with obvious bradykinesia and frequent postural tremor (Table 1). Despite the fact that their parkinsonian clinical syndrome remained moderate (neither monkey required tube feeding at any stage), animals presenting a clinical score >3 were no longer capable of correctly performing the task (2% success rate). Kinematic parameters were not calculated because of the low success rate (Table 2).

**Microstimulation data**

The motor response evoked by intracortical microstimulation (ICMS) was used to delimit the boundary between the pre-SMA and the SMAp and chart somatotopic
organization within each structure. In pre-MPTP animals the pre-SMA was characterized by the fact that motor response to ICMS was rare (Fig. 2A) and at a high threshold (>50 μA).

Table 2 Behavioural data

<table>
<thead>
<tr>
<th></th>
<th>Before MPTP</th>
<th>Presymptomatic</th>
<th>Symptomatic</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(n = 12 721)</td>
<td>(n = 5494)</td>
<td>(n = 2689)</td>
</tr>
<tr>
<td>Correct response (%)</td>
<td>82.0</td>
<td>51.0***</td>
<td>2.0**</td>
</tr>
<tr>
<td>Error of direction (%)</td>
<td>7.6</td>
<td>5.0**</td>
<td>1.0***</td>
</tr>
<tr>
<td>Non movement (%)</td>
<td>10.0</td>
<td>36.0**</td>
<td>96.6***</td>
</tr>
<tr>
<td>Insufficient amplitude (%)</td>
<td>0.4</td>
<td>8.0**</td>
<td>0.4</td>
</tr>
<tr>
<td>RT (ms)</td>
<td>491 ± 10</td>
<td>479 ± 7</td>
<td>NC</td>
</tr>
<tr>
<td>MT (ms)</td>
<td>309 ± 12</td>
<td>362 ± 18*</td>
<td>NC</td>
</tr>
<tr>
<td>RW (ms)</td>
<td>624 ± 59</td>
<td>472 ± 53</td>
<td>NC</td>
</tr>
<tr>
<td>RTi (ms)</td>
<td>742 ± 42</td>
<td>1653 ± 54*</td>
<td>NC</td>
</tr>
</tbody>
</table>

n = number of trials. Top: percentage of response; incorrect response includes errors of direction, absence of motor response (non movement) or movement of insufficient amplitude. Bottom: kinematic data, i.e. average time (in ms) ± SD. Data from both monkeys were pooled. *P < 0.05, **P < 0.001; NC = not calculated because of the low rate of correct responses.

Fig. 2 Responses to microstimulation. (A) Left: top view of the area of the mesial frontal cortex recorded in this study. Dotted line: location of the recording chamber; rectangle: recording area (dotted zone: pre-SMA; striped zone: SMAp). PS: principal sulcus; ARC: arcuate sulcus; CS: central sulcus; ML: medial line. Right: an enlarged schema of the frontal mesial cortex indicates the response to microstimulation. The size of each figure is proportional to the number (n) of recorded neurons responding or not responding to microstimulation. Data for the two monkeys were pooled for each map. (B) Graph representing the percentage of neurons responding to intra-cortical microstimulation (ICMS) in the arm region in each area. (C) Graph representing the threshold intensity of ICMS in each area. *P < 0.01; **P < 0.0001.

There were few somatosensory proprioceptive fields in this area (data not shown). SMAp neurons, on the other hand, were easily excitable (<50 μA) and response to sensory stimulation was frequent. There was no significant difference
in the percentage of response to microstimulation in the pre-SMA between the pre-MPTP, presymptomatic and symptomatic situations. In the SMAp, however, this percentage decreased drastically in the symptomatic situation (Fig. 2B). The threshold of response to ICMS (Fig. 2C) increased in both the pre-SMA and the SMAp, not only in the symptomatic but also in the presymptomatic situation \[ F(5,155) = 12.7; \, P < 0.0001 \].

Neuronal recording data
We restricted the recording zone to the arm regions of the pre-SMA and SMAp. A total of 520 SMA neurons were recorded in this zone, which was exactly the same for the three situations. Two hundred and ninety-two neurons were located in the pre-SMA (113 in the normal situation, 77 in the presymptomatic and 102 in the symptomatic situation), and 228 in the SMAp (89 in the normal, 42 in the presymptomatic and 97 in the symptomatic situation).

For the first stage of the task (reference period) a two-way ANOVA for the three situations and two areas showed significant differences in neuronal firing frequency \[ F(5,446) = 2.5, \, P < 0.05 \], which decreased in the pre-SMA in both the presymptomatic (4.4 ± 2.3 spikes/s, \( P = 0.007 \)) and the symptomatic (4.4 ± 2.2 spikes/s, \( P < 0.01 \)) situation compared with the pre-MPTP situation (5.6 ± 3.5 spikes/s).

There was no variation in the firing frequency of SMAp neurons during the reference period between the three situations.

Modifications of neuronal activity during instruction and delay periods
A progressive modification of neuronal activity during the successive stages of the task was observed from the pre-MPTP to the presymptomatic and the symptomatic situation. Examples of neuronal activity in the pre-SMA during the instruction period of the task for the three different situations are shown in Fig. 3.

The relative modification of firing rate in response to the onset cue varied for each situation \[ F(5,445) = 9.8, \, P < 0.0001 \], as did the response to target presentation \[ F(5,445) = 10.1, \, P < 0.0001 \].

Firing rate was higher in the pre-SMA than in the SMAp (Fig. 4A and B) in response to both the onset cue \( P < 0.01 \) and target presentation \( P < 0.05 \). For the onset cue, firing rate decreased in the pre-SMA both in the presymptomatic and the symptomatic situation versus the pre-MPTP situation (Fig. 4A). The modification of firing rate was less pronounced in the SMAp. After target presentation, firing rate decreased significantly in both the pre-SMA and the SMAp (Fig. 4B). This diminution was already significant in the pre-SMA in the presymptomatic situation.

Our second analysis considered only those neurons that modified their activity in correct trials (Fig. 4C and D). The activity of these neurons was also studied during the trials in which they did not effect the required movement (Fig. 4E and F). Pre-SMA neurons responded more frequently to visual cues (Fig. 4C and D) than SMAp neurons (\( \chi^2 = 7.9, \, P < 0.01 \)). The percentage of neurons which responded to the onset cue in correct trials decreased in both the pre-SMA and the SMAp in presymptomatic monkeys (Fig. 4C). In symptomatic monkeys, none of these neurons modified their activity during the rare trials that were performed correctly. The percentage of response to target presentation in correct trials also decreased in the SMAp of presymptomatic monkeys (Fig. 4D).

The percentage of response to the onset cue and target presentation was not the same in correct trials and in trials without movement, whatever the situation (compare Fig. 4C and D with 4E and F). Before MPTP, the difference in the percentage of response to the onset cue between correct trials and trials without correct movement was particularly marked in the pre-SMA (\( \chi^2 = 16.2, \, P < 0.001 \)), and to a lesser extent in the SMAp (\( \chi^2 = 4.4, \, P < 0.05 \)). A similar difference was observed in the response to target presentation (pre-SMA: \( \chi^2 = 23, \, P < 0.001 \); SMAp: \( \chi^2 = 18, \, P < 0.001 \)).

Modifications of neuronal activity were observed during the delay period in 25% of pre-SMA neurons (e.g. Fig. 5A–C) and 19% of SMAp neurons (e.g. Fig. 5A′–C′).

Few neurons responded in the symptomatic situation. No significant difference in the percentage of neurons presenting a modification of activity during this period was observed in correct trials between the pre-MPTP and the presymptomatic situation (Fig. 5D). In the symptomatic situation no neuron modified its activity during this period. In trials without correct movement the percentage of neurons modifying their activity even decreased (Fig. 5E). Both in the pre-SMA and the SMAp the percentage of neurons modifying their activity during the delay period was lower in trials without correct movement than in correct trials.

Modifications of neuronal activity during behavioural response period
Monkeys did not move until the Go signal appeared. At this point the activity of certain neurons changed and remained modified throughout the movement period. It was therefore difficult to dissociate, for most neurons, the activity reflecting a response to the Go signal from that related to movement preparation. Examples of neuronal activity for the three situations, pre-MPTP, presymptomatic and symptomatic, are shown in Fig. 6.

Statistical analysis of the relative frequency of neuronal activity modified after the Go signal, calculated from all recorded neurons, showed significant differences \[ F(5,445) = 12.1, \, P < 0.0001 \]. This parameter decreased drastically in both the pre-SMA and the SMAp in the symptomatic monkey (Fig. 7A). It was diminished in the presymptomatic monkey in the SMAp but not in the pre-SMA.
The percentage of neurons presenting movement-related activity in correct trials was lower in both areas in the presymptomatic than in the pre-MPTP situation (Fig. 7B). In trials without correct movement this percentage only decreased in the symptomatic situation (Fig. 7C). In the pre-MPTP situation there was a significant difference (compare Fig. 7B with C) in the percentage of correct and incorrect responses between the pre-SMA ($\chi^2 = 73.0$, $P < 0.001$) and the SMAp ($\chi^2 = 98.6$, $P < 0.001$).

Differences were also observed for the temporal parameters of neuronal activity following the Go signal between the three situations [$F(3,231) = 7.0$, $P < 0.001$].

CRT (Fig. 8A) increased in the presymptomatic monkey in the pre-SMA ($P < 0.0001$) but not in the SMAp. In the normal monkey, reaction time was slightly shorter in the pre-SMA than in the SMAp, but the difference was not statistically significant. Premotor time was shorter [$F(3,239) = 5.1$, $P < 0.01$] in the pre-SMA (Fig. 8B) in the presymptomatic than in

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**Fig. 3** Neuronal activity of the pre-SMA during the instruction period of the task. Examples of pre-SMA neurons which modified their activity in response to the onset cue (A–C) and target presentation (A’–C’). The activity of each neuron is time-locked to the onset signal (O) in A–C and to target presentation (T) in A’–C’. Neuronal activity is represented in the form of a raster display (top, each point is an action potential, each line a different trial) and a histogram of firing frequency over time (bottom, bin width 50 ms).
Onset cue | Target
---|---

All recorded neurons

![Graph showing relative firing frequency](image)

Correct trials

![Graph showing percentage of response](image)

Trials without movement

![Graph showing percentage of response](image)

**Fig. 4** Analysis of modification of neuronal activity during the instruction period of the task. (A, B) Relative firing frequency (%), i.e. ratio of neuronal firing frequency following onset cue (A) or target presentation (B) to neuronal firing frequency during the reference period, calculated for all recorded neurons. (C, D) percentage of neurons which modified their activity after the onset cue (C) and target presentation (D) in correct trials. (E, F) percentage of neurons which modified their activity after the onset cue (E) and target presentation (F) in trials without correct movement. *$P < 0.05$; **$P < 0.001$; °, the sample was too small for statistical analysis.

In the pre-MPTP situation ($P < 0.01$), but did not vary significantly in the SMAp. In the normal monkey there was no significant difference between the pre-SMA and the SMAp for premotor time ($P > 0.05$). The duration of the period during which there was a modification of neuronal activity was longer (Fig. 8C) in the presymptomatic than in the pre-MPTP situation [$F(3,232) = 5.6, P < 0.01$), particularly in the SMAp ($P < 0.001$).

In both the presymptomatic and the symptomatic situation, neuronal firing pattern varied considerably from one trial to another in both the pre-SMA and the SMAp, giving an aspect of erratic activity. Typical raster displays for three SMAp neurons are given in Fig. 9A–C.

In order to quantify this variability we calculated for each trial the ratio of the mean standard deviation of inter-spike interval to the mean inter-spike interval. The value of this ratio increased significantly in both areas in the symptomatic, and even in the presymptomatic situation (Fig. 9D).

**Histological data**

The post mortem examination of mesencephalic slices (Fig. 10) from the brains of the two monkeys showed a 93% decrease in the number of tyrosine hydroxylase positive neurons in the substantia nigra pars compacta and a 69% decrease in the ventral tegmental area (VTA) compared with slices taken from control animals ($P < 0.001$).

**Discussion**

Our data provide direct evidence at cellular level that neuronal activity in the medial wall is modified in the...
parkinsonian situation. Not only was the SMAp less excitable in response to microstimulation, both the firing rate and the percentage of responding neurons tended overall to decrease in the pre-SMA and the SMAp as the pathology progressed. These electrophysiological data concord with reports showing a decrease in cerebral blood flow in the SMA of parkinsonian patients during the execution of a motor task (Eidelberg et al., 1990; Jenkins et al., 1992; Rascol et al., 1992, 1994, 1998; Playford et al., 1993; Jahanshahi et al., 1995; Samuel et al., 1997; Catalan et al., 1999). We found, in
addition, that dysfunction was particularly pronounced in the pre-SMA, as has been suggested by recent fMRI studies (Sabatini *et al*., 2000; Haslinger *et al*., 2001). Even more surprising was the fact that neuronal activity was diminished and disorganized both during the instruction and the behavioural stages of the delayed motor task. All the different stages of the motor planning process are therefore likely to be affected: analysis of instructions, preparation and initiation of movement. In both the pre-SMA and the SMAp the progressive decrease in neuronal response paralleled the clinical appearance and development of akinesia. What, then, is the link between the neuronal dysfunction we observed in both these areas and the pathogenesis of akinesia? Two non-exclusive mechanisms may play a role: (i) a decrease in the ability to correctly respond to pertinent information required for elaboration of the motor program; (ii) an inability to action this motor program at the right moment. The pre-SMA and the SMAp would appear to be implicated in both these mechanisms.

**Definition of the presymptomatic and symptomatic states**

The schedule of MPTP intoxication chosen for this study was particularly slow and progressive; this allowed us to distinguish a presymptomatic and a symptomatic situation. Each monkey’s clinical state was assessed daily on the basis of a clinical rating scale specifically adapted for monkeys (Benazzouz *et al*., 1992). Following the classification adopted by previous authors (Bezard *et al*., 2001b), we considered an animal was presymptomatic as long as his daily MCRS score was ≤3. The mean value of this score for both our animals for the presymptomatic stage was in fact extremely low (0.49 ± 0.70). However, although animals’ spontaneous behaviour in their cages was virtually the same at this stage as that of a normal monkey, their level of performance during the task had already deteriorated. From this point of view, they could be regarded as already presenting a very mild form of parkinsonism. Once they reached the symptomatic stage, the level of performances then fell drastically. It is likely that, by this stage, SNc neuronal loss had reached the point at which compensatory mechanisms can no longer mask the parkinsonian syndrome. In humans, it is thought that parkinsonian clinical symptoms appear when dopaminergic neuronal death exceeds a critical threshold which corresponds to a loss of ~60% of SNc pericaryons (Bernheimer *et al*., 1973; Riederer and Wuketich, 1976), after a preclinical phase of variable duration (Agid, 1991; Fearnley and Lees, 1991; Koller, 1992; Morrish *et al*., 1996). As far as our symptomatic monkeys are concerned, it would seem very likely, however, that their low level of performance was not due only to bradykinesia. Their spontaneous locomotor activity in their cages, for example, was still only moderately impaired and neither animal required tube feeding, a procedure frequently

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**Fig. 6** Neuronal activity during the behavioural period of the task. Examples of neuronal activity in the pre-SMA (left) and SMAp (right) in the three different situations. In each case, the activity of each neuron is time-locked either to the Go signal (G), or to movement onset (M). Neuronal activity is represented in the form of a raster display (top) and histogram (bottom, bin width 50 ms). In most cases, symptomatic monkeys did not perform the movement (No movement).
necessary in MPTP-treated monkeys. It is possible that motivation, attention or working memory may also be affected. The fact that there was extensive dopaminergic cell death in the VTA suggests that information processing in the meso-cortical pathway may also be impaired. This point will be discussed below.

**The decrease in neuronal response during the instruction period of the task**

Both in the symptomatic and the presymptomatic situation the firing rate of pre-SMA neurons diminished during the initial reference period of the task. There was also a decrease in the firing rate of pre-SMA and SMAp neurons in response to visual instruction cues (onset cue and target presentation). This modification was particularly marked in the pre-SMA, an area which receives direct inputs from the prefrontal cortex (Luppino et al., 1990, 1993; Bates and Goldman-Rakic, 1993; Morecraft and Van Hoesen, 1993; Lu et al., 1994). Several studies have shown that pre-SMA neurons respond to visual cues giving instructions for movement execution (Matsuzaka et al., 1992; Tanji, 1994). The fact that the percentage of pre-SMA neurons responding to visual cues was higher in trials with correct movement than in trials without movement suggests that the decrease in the response to visual cues could be related to a low level of attention. We have already reported similar data in a previous study based on a more complex task (Akkal et al., 2002). The SMAp, on the other hand, would appear to be less influenced by visual inputs (Shima et al., 1996; Tanji, 1996). There were, however, some SMAp neurons which modified their firing rate in response to onset cue and target presentation. Although there are few projections from the pre-SMA to the SMAp (Luppino et al., 1990, 1993), those that exist may convey visual inputs to the SMAp.

The role played by the pre-SMA in attention shifting has already been reported in the monkey (Matsuzaka and Tanji, 1996; Shima et al., 1996; Nakamura et al., 1998; Shima and Tanji, 2000). Abnormal activity in the pre-SMA could thus
impair the attentional process during execution of the motor task. The considerable variations in neuronal activity observed from one trial to another in the symptomatic, and even presymptomatic, situation were clinically uncorrelated to fluctuations in vigilance and could reveal temporal variations in the quality of the attention animals were paying to the task. A second possibility is that the motivation of MPTP-treated monkeys to perform the task was diminished. It is well known that dopamine depletion induces an impairment of the motivational processes underlying appetitive learning in animals (Robbins and Everitt, 1996). These cognitive deficits have frequently been observed in Parkinson’s disease (Sprengelmeyer et al., 1995). A recent PET study has also shown a reduction in the activity of the medial frontal gyrus and the anterior cingulate gyrus during reward processing in the brain of parkinsonian patients (Kunig et al., 2000).

What is particularly striking is that the response of pre-SMA neurons to instruction cues was abnormal even in the presymptomatic monkey, despite the fact that these animals presented virtually no clinical signs during daily assessment in their cages. It is, however, possible that this neuronal dysfunction may become clinically apparent if monkeys are faced with a more demanding cognitive task. Numerous studies on humans suffering from Parkinson’s disease have reported that patients are more severely handicapped when they have to cope with more complex tasks (Cooper et al., 1994).

The task we gave our monkeys was non-sequential and this may well explain the relatively low percentage of neurons which modified their activity during the delay period. A number of reports have highlighted the role played by the pre-SMA and the SMAp in the execution of complex and/or sequential tasks (Tanji and Mushiake, 1996; Nakamura et al., 1998; Shima and Tanji, 2000), but these regions are also known to be activated during simple motor tasks, especially when these arise from internal intent (Tanji and Mushiake, 1996; Sakai et al., 1999; Picard and Strick, 2001). In our study, the percentage of neurons that modified their activity during the delay period hardly varied from the pre-MPTP to the presymptomatic situation. This percentage dropped close to zero in the symptomatic situation but successful trials were too rare to draw direct conclusions concerning a possible defect in working memory which could impede monkeys’ performances. This point requires further experimentation. A putative role of the pre-SMA in spatial working memory has been proposed (Petit et al., 1998), and we do know that parkinsonian patients suffer from working memory disorders (Graceffa et al., 1999; Kikuchi et al., 2001; Cox et al., 2002; Jahanshahi et al., 2002).

The decrease in neuronal response during the behavioural period of the task

Before discussing the modifications observed in neuronal activity during the behavioural stage of the task, it is interesting to note that, both in the symptomatic and the presymptomatic situation, there was a decrease in the SMAp response to microstimulation. The type of response that is common in the normal monkey (Mitz and Wise, 1987; Luppino et al., 1991) was hard to obtain in the lesioned animal, even with a higher intensity of current. This would clearly indicate that the SMAp is underactive in the
parkinsonian state. Although it is difficult to draw a direct parallel with studies using transcranial magnetic stimulation (TMS) in humans, it is worth noting that the movements of patients suffering from Parkinson’s disease are disrupted when single pulse TMS is applied over the SMA during the early stages of the movement, whereas the movements of control subjects are not affected by a single application (Cunnington et al., 1996). Repetitive TMS on this region, on the other hand, does interfere with the organization of complex motor sequences in control subjects (Gerloff et al., 1997; Boylan et al., 2001). The physiological effects of repetitive TMS remain unclear (Modugno et al., 2001; Touge et al., 2001), but it is likely that it inhibits the normal functioning of the frontal mesial cortex (Cunnington et al., 1996; Gerloff et al., 1997; Boylan et al., 2001). It is therefore particularly interesting to note the hypoexcitability of these regions in the lesioned animal observed in our study. These data could well afford a partial explanation at least for the deleterious effect of repetitive TMS in parkinsonian patients.

In the SMAp, CRT did not vary significantly but the percentage of responding neurons decreased, even in the presymptomatic situation. It has recently been shown, in a report using the 2-DG metabolic mapping technique, that a decrease in the rate of metabolism in the SMAp only appears when MPTP-treated monkeys become fully parkinsonian (Bezard et al., 2001a). It is, however, difficult to draw a direct parallel between these results and ours when experimental conditions are so different. The schedule of intoxication we adopted was particularly progressive. Even when behavioural reaction time and clinical examination were normal, the movement time of our presymptomatic monkeys increased and their levels of performance fell slightly. This could

Fig. 10 Quantiﬁcation of dopamine cell loss. Combined tyrosine hydroxylase and Nissl staining of dopaminergic neurons in the substantia nigra pars compacta (SNC) and the VTA. Top (A–F): histological sections; bottom (G): quantiﬁcation of mesencephalic dopaminergic neurons in the SNC (squares) and the VTA (crosses). (A, B) Control monkey; (C, D) MPTP-treated monkey 1; (E, F) MPTP-treated monkey 2. Mean ± SEM number of TH-positive neurons on three representative sections. (G) Mean number of tyrosine hydroxylase-positive labelled neurons. **p < 0.001.
indicate that there are already precursory signs of bradykinesia at this stage. There is also the fact that electrophysiological techniques, which give an instantaneous picture of neuronal function, may detect phasic changes in neuronal activity with more precision than metabolic techniques. We also observed that the modification of neuronal activity after the Go signal lasted longer in the presymptomatic than in the pre-MPTP situation. A failure to appropriately terminate SMA activity has already been reported both in studies on human patients, using movement-related potential recording (Cunnington et al., 1995) and in monkeys, using unit recording (Watts and Mandir, 1992). It is thought that this dysfunction may result from the failure of an internal cue to terminate sustained activity in the SMA for the impending movement (Brotchie et al., 1991). In our study, even in the presymptomatic situation, monkeys required more time to return the lever to its initial position. We cannot, however, disregard the possibility that the prolonged activity of SMAp neurons is due to proprioceptive afferents, which are known to influence neuronal activity in the SMAp (Tanji, 1994; Picard and Strick, 1996).

The percentage of pre-SMA neurons that modulated their activity after the Go signal also diminished in the presymptomatic situation, whilst CRT increased. The fact that the response of presymptomatic pre-SMA neurons to instruction cues was also lower could suggest that this increase in CRT may be due, in part at least, to the diminished response to the Go signal. It is probably through an indirect pathway that the pre-SMA influences the motor system, since there are few projections from the pre-SMA to the SMAp and none at all to the primary motor cortex or the spinal cord (Luppino et al., 1990, 1993; Dum and Strick, 1991; He et al., 1995). The pre-SMA could, however, influence the motor cortex through its connections with the rostral cingulate cortex (Luppino et al., 1990, 1993; Bates and Goldman-Rakic, 1993; Morecraft and Van Hoesen, 1993; Lu et al., 1994), a structure that is densely connected with the SMAp (Wang et al., 2001).

**The effect and origin of dopamine cell loss**

It would seem very probable that the underactivity of the pre-SMA and SMAp in the parkinsonian monkey is a consequence of the dopamine cell loss that characterizes Parkinson’s disease. Several lines of evidence, in both animals (Robbins and Everitt, 1987; Sawaguchi et al., 1990) and humans (Daniel et al., 1991; Mattay et al., 1996, 2000), suggest that the focusing function of dopamine relies on the enhancement of the signal-to-noise ratio of specific neuronal patterns (Cools et al., 2002). Our results indicate not only that neuronal activity decreased in response to significant events, but also that a disorganized neuronal pattern with fluctuations in frequency unrelated to any behavioural events emerged. Moreover, phasic changes in neuronal activity appeared to be less strictly delimited in time. This temporal dispersion of the message is likely to compromise neuronal processing within the frontal mesial cortex.

There are two pathways through which dopamine cell loss can influence cortical neuronal activity: either directly via meso-cortical dopaminergic system (Thierry et al., 1973; Le Moal and Simon, 1991; Schultz, 1998) or indirectly through the striato-pallido-thalamocortical loop (Albin et al., 1989; Alexander and Crutcher, 1990; DeLong, 1990). It is possible that both these mechanisms may be affected. The cognitive deficit presented by parkinsonian patients has been attributed, at least in part, to a dysfunction of the mesocortical dopaminergic system (Rogers et al., 1987; Cooper et al., 1994; Cools et al., 2001b, 2002). Our results showed that, in the parkinsonian monkey, the number of dopaminergic neurons decreased both in the substantia nigra pars compacta (A9) and the TVA (A10). The meso-cortical tract that originates in the TVA (Simon and Le Moal, 1988; Schultz, 1998) generously innervates the frontal cortex (Berger et al., 1991; Williams and Goldman-Rakic, 1993). It is already known that dopamine modulates information processing in this region of the brain both in monkeys (Brozoski et al., 1979; Williams and Goldman-Rakic, 1995; Arnsten, 1998) and in humans (Daniel et al., 1991; Friston et al., 1992; Grasby et al., 1992; Mattay et al., 1996, 2000; Cools et al., 2001a). A cortical deficit in dopamine could in itself contribute to the underactivity of both pre-SMA and SMAp neurons observed in our lesioned monkeys. It is interesting to compare the electrophysiological data we collected with the clinical scores of our animals. At the symptomatic stage, monkeys were incapable of performing the task correctly but presented only moderate bradykinesia in their home cages. This suggests that their low level of performance could possibly be explained by an impairment of the motivational and/or attention process, possibly induced by a dysfunction of the meso-cortical pathway. The other way in which cortical activity could be influenced by dopamine cell loss would be by a decrease in striatal dopamine release, inducing a disequilibrium between the direct and indirect striato-pallidal pathways. The resulting hyperactivity of the internal pallidum could brake neuronal activity in the SMA by inhibiting the motor thalamus (Albin et al., 1989; Alexander and Crutcher, 1990; DeLong, 1990; Wichmann and DeLong, 1996). This phenomenon would mainly concern the SMAp, which receives inputs from the basal ganglia through the ventral lateral nucleus of the thalamus, and far less the pre-SMA, which receives very few inputs (Scholl and Strick, 1984; Dum and Strick, 1991; Matelli and Luppino, 1996; Sakai et al., 2000). The dysfunction observed in the activity of pre-SMA neurons is therefore more probably due to a cortical deficit in dopamine. This point requires further investigation.

**What role could the pre-SMA and SMAp play in the pathogenesis of akinesia?**

Our results indicate that neuronal activity in the pre-SMA and the SMAp is severely depressed in the parkinsonian situation.
Although it is likely that other cortical or subcortical regions are involved in the pathophysiology of akinesia (Hirsch et al., 2000; Pahapill and Lozano, 2000; Berardelli et al., 2001), the pivotal position of the pre-SMA and SMAp between the prefrontal and motor cortical areas makes it probable that these structures play an essential role in this pathological process.

Dopamine cell loss impairs, directly or indirectly, the focused processing of information in the pre-SMA. Since pre-SMA neurons become incapable of distinguishing signal from noise, the threshold level of activation required to correctly respond to external instructions is no longer attained. Whether this phenomenon originates in the pre-SMA or the prefrontal cortex, which projects to the pre-SMA (Bates and Goldman-Rakic, 1993; Luppino et al., 1993), is not yet known. It is possible that there may be a modification of neuronal activity in the dorsolateral prefrontal cortex similar to the modification we observed in the frontal mesial cortex. Two recent functional imaging studies, which report a decrease in the efficiency of prefrontal cortical information processing in untreated parkinsonian patients (Cools et al., 2002; Mattay et al., 2002) would support the second hypothesis. Parkinsonian patients are known to suffer from frontal cognitive deficits and have trouble performing attentional shifting tests (Owen et al., 1992, 1993; Cooper et al., 1994; Robbins et al., 1994; Bennett et al., 1995; Sprengelmeyer et al., 1995; Cools et al., 2001a, b). Such a mechanism could play a critical role in the pathophysiology of akinesia, when the subject has to adequately chain a series of movements. Paradoxically, however, movement performance in Parkinson’s disease patients is dramatically improved in the presence of external cues (Georgiou et al., 1993). It is thought that abnormal basal ganglia function impairs the reception and treatment of internal information destined to improve the performance of a movement (Cunnington et al., 1995). Visual stimuli may help, to some extent, to initiate movement in these patients (Praamstra et al., 1998; Azulay et al., 1999). This process, which requires a particular mobilization of the patient’s attention, may, however, be a compensatory mechanism. The impairment of information processing within the pre-SMA probably affects a more executive aspect of motor planning, by perturbing the transfer of information between the prefrontal cortex and premotor areas.

A dysfunction in the pre-SMA could potentially depress the activation of SMAp neurons. There would seem, however, to be few direct projections from the former to the latter (Luppino et al., 1990, 1993; Dum and Strick, 1991; He et al., 1995). This leaves the possibility that the pre-SMA and the SMAp process different types of information in parallel. The fact that CRT and premotor time were the same in both areas would argue in favour of this hypothesis. We found that the SMAp is underactive at the critical moment when the instruction to move is given. This is highly likely to directly affect the motor planning process, since the SMAp is known to be involved in movement preparation and initiation (Matsuzaka and Tanji, 1996; Shima et al., 1996; Tanji, 1996; Tanji and Mushiake, 1996; Nakamura et al., 1998). It also sends strong inputs to the primary motor cortex (Luppino et al., 1990, 1993; Bates and Goldman-Rakic, 1993; Morecraft and Van Hoesen, 1993; Lu et al., 1994; Matsuzaka and Tanji, 1996). There is therefore every chance that neuronal activity in the latter will be impaired in consequence. Experimental data revealing a dysfunction of the primary motor cortex in the MPTP-treated monkey (Doudet et al., 1990; Watts and Mandir, 1992) and electrophysiological data in human patients (Defebvre et al., 1996; Magnani et al., 1998; Brown and Marsden, 1999) would endorse this hypothesis. Similar proposals have been made regarding bradykinesia, another of the cardinal manifestations of Parkinson’s disease. In a recent review article, the authors note the inadequate reportecl in parkinsonian patients between desired movement parameters and the underscaled dynamic force produced and argue that bradykinesia could result from a failure of basal ganglia output to reinforce the cortical mechanisms that prepare and execute the commands to move (Berardelli et al., 1986, 2001). SMAp dysfunction could well play a critical role in this process. Not only is the focused selection of incoming information in the pre-SMA and SMAp impaired, the actual capacity of the neurons of both regions to deal with the information they receive also deteriorates. The conjunction of these phenomena could, at least in part, play a critical role in the pathogenesis of akinesia.

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