An Effect of Dopamine Depletion on Decision-making: The Temporal Coupling of Deliberation and Execution

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Abstract

■ When a decision between alternative actions has to be made, the primate brain is able to uncouple motor execution from mental deliberation, providing time for higher cognitive processes such as remembering and reasoning. The mental deliberation leading to the decision and the motor execution applying the decision are likely to involve different neuronal circuits linking the basal ganglia and the frontal cortex. Behavioral and physiological studies in monkeys indicate that dopamine depletion may result in a loss of functional segregation between these circuits, hence, in interference between the deliberation and execution processes. To test this hypothesis in humans, we analyzed the movements of parkinsonian patients in a go/no-go task, contrasting periods of uncertainty with periods of knowledge about the rule to be applied. Two groups of patients were compared to healthy subjects: one group was treated with dopaminergic medication and the other with deep brain stimulation; both groups were also tested without any treatment. In healthy subjects, the movement time was unaffected by uncertainty. In untreated patients, the movement time increased with uncertainty, reflecting interference between deliberation and execution processes. This interference was fully corrected with dopaminergic medication but was unchanged with deep brain stimulation. Moreover, decision-related hesitations were detectable in the movements of dopamine-depleted patients, revealing a temporal coupling of deliberation and execution. We suggest that such coupling may be related to the loss of dopamine-mediated functional segregation between basal ganglia circuits processing different stages of goal-directed behavior. ■

INTRODUCTION

Experienced chess players do not deliberate before deciding on their moves until the game is well advanced. The question is whether their gestures are different at the latter stages of the game, when they deliberate about the moves, compared with the start, when they execute known moves. If the answer is no, we must assume that a player is able to uncouple motor execution from mental deliberation. Our working hypothesis is that healthy players do have such an ability, which relies on the release of dopamine (DA) within the basal ganglia (BG). Furthermore, the role of DA in uncoupling execution from deliberation could be extended to every situation where a decision between alternative actions has to be made.

Arguments supporting this hypothesis are mainly drawn from experiments on nonhuman primates. Axonal tracing studies have revealed that several parallel circuits, starting and ending in the frontal cortex, can be followed through BG structures, such as the striatum and the pallidum (Alexander, DeLong, & Strick, 1986; Selemon & Goldman-Rakic, 1985). Depending on the cortical input to the striatum, each circuit is likely to participate in a specific functional field: for instance, reward processing for the orbito-frontal and anterior cingulate cortices (Shidara & Richmond, 2002; Tremblay & Schultz, 1999), working memory for the dorsolateral prefrontal cortex (Funahashi, Chafee, & Goldman-Rakic, 1993), or movement execution for the motor and premotor cortices (Kakei, Hoffman, & Strick, 2001; Kakei, Hoffman, & Strick, 1999). Human brain imaging studies have shown that instructed movement execution activates a network including the posterior putamen as well as the sensorimotor and premotor cortices, whereas self-selected movement execution additionally includes the caudate nucleus and the anterior putamen as well as the anterior cingulate and dorsolateral prefrontal cortices (Gerardin et al., 2004; Jenkins, Jahanshahi, Jueptner, Passingham, & Brooks, 2000; Jueptner, Frith, Brooks, Frackowiak, & Passingham, 1997; Jahanshahi et al., 1995). Deliberation and execution are therefore likely to involve distinct but neighboring circuits within the

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BG. However, the segregation of BG circuits is the subject of debate, because of the overlapping dendritic and axonal arborizations between functional territories (Haber, 2003; Graybiel, Aosaki, Flaherty, & Kimura, 1994). An elegant solution to the debate has been proposed: The relative independence of BG circuits would be modulated by the dopaminergic system (Bergman et al., 1998; Filion, Tremblay, Matsumura, & Richard, 1994), so that DA depletion would result in interferences between the deliberation and execution processes.

In line with this, we have already reported that in monkeys with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced DA depletion, the engagement of cognitive processes exacerbated disorders that could be considered as motor, such as hesitations and freezings (Pessiglione, Guehl, Hirsch, Feger, & Tremblay, 2004). Parkinson's disease (PD), which is essentially caused by degeneration of mesencephalic DA neurons, offers an opportunity to study human brain functioning with different DA levels. Indeed, the effect of L-Dopa medication can be compared with that of deep brain stimulation of the subthalamic nucleus (STN-DBS), to assess the specific effects of DA depletion and replacement. The two treatments improve parkinsonian motor symptoms, namely, akinesia, rigidity, and tremor (Kumar et al., 1998; Limousin et al., 1998), but only L-Dopa is considered to restore DA levels (Hilker et al., 2003; Strafella, Sadikot, & Dagher, 2003). Testing the uncoupling of deliberation and execution requires observing manual performance in decision-making situations. Both manual performance and decision-making have been extensively studied in PD, but in separate experiments. Indeed, studies that used tasks involving decision-making, such as gambling and probabilistic or reversal learning tasks (Czernecki, Pillon, Houeto, Pochon, et al., 2002; Cools, Barker, Sahakian, & Robbins, 2001; Knowlton, Mangels, & Squire, 1996), focused on erroneous responses, without any mention of parameters relating to movement execution. When durations are mentioned, they refer to response times, failing to distinguish between reaction time (RT) and movement time (MT), hence, between deliberation and execution processes.

In the present study, manual performance was analyzed during a go/no-go task requiring a decision between two alternative actions: to touch or not to touch a computer screen. Subjects must find out by trial and error the rule governing the appropriate action for each of the two stimuli. Once the rule has been correctly applied during several trials, it is automatically changed without warning. Thus, the level of uncertainty oscillates during the task between periods when subjects search for a new rule and periods when they apply the rule they have just found out. Before movement execution, a ''searching'' trial involves different processes subsumed under the term ''deliberation'' (e.g., working memory, rule extraction, or outcome prediction), in addition to the processes required by an ''applying'' trial (e.g., stimulus discrimination or movement selection). Hence, contrasting the searching with the applying periods allows the impact of deliberation on movement execution to be isolated. To evaluate such an impact, the trajectory and the velocity profile of reaching movements were reconstructed using image analysis software. These movement characteristics were then compared between untreated, medicated, and stimulated PD patients, as well as with matched control subjects. According to our hypothesis, execution would be unaffected by deliberation in the event of intact (control subjects) or restored (medicated patients) DA levels, but perturbed in the event of DA depletion (unmedicated patients, with or without STN-DBS).

RESULTS

Three groups of subjects (Table 1) were assessed twice on the go/no-go task (Figure 1): control subjects, PD patients tested Off and On L-Dopa only (PD-Dopa group), and PD patients tested Off and On STN-DBS only (PD-Stim group). For each subject, the series of correct trials preceding rule change were assigned to the applying period, and the other trials to the searching period. For all experimental variables, the effects of group (control, PD-Dopa, and PD-Stim), repetition (first and second assessments), and uncertainty (searching and applying periods) were tested with an analysis of variance. In the absence of repetition effects, the data from the two assessments were then pooled (Table 2) for post hoc comparisons between all subgroups (control, Off-Dopa, On-Dopa, Off-Stim, On-Stim) and be-

Table 1. Main Characteristics of PD Patients and Control Subjects

Group	*Control*	*PD-Dopa*	*PD-Stim*
Sex (M/F)	8/10	9/9	9/9
Age (years)	61.8 ± 2.1	59.0 ± 1.7	56.6 ± 1.7
Education (years)	13.2 ± 0.8	11.6 ± 0.7	11.2 ± 0.8
Mattis DRS (out of 144)	142.5 ± 0.5	140.1 ± 0.8	141.3 ± 0.6
MADRS (out of 60)	3.2 ± 0.9	8.1 ± 1.7	7.4 ± 1.6
Disease duration (years)	–	15.3 ± 1.7	14.7 ± 1.6
UPDRS ''OFF''	–	36.8 ± 2.7	34.9 ± 3.1
UPDRS ''ON''	–	11.5 ± 2.4	12.9 ± 3.1

Values are expressed as mean ± SEM. The motor disability scores (UPDRS) correspond to the clinical states in which patients were tested on the go/no-go task. UPDRS = Unified Parkinson's Disease Rating Scale; DRS = Dementia Rating Scale; MADRS = Montgomery and Asberg Depression Rating Scale.

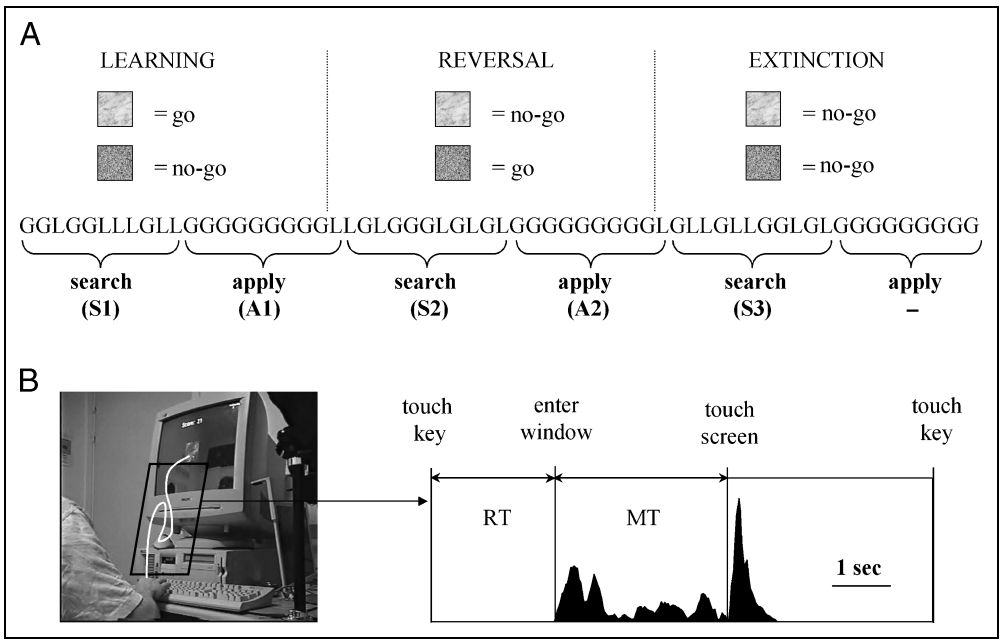

Figure 1. Experimental design. (A) The go/no-go Task. Searching and applying periods were distinguished within each of the three rules (learning, reversal, extinction) that specify the value (go or no-go) of the two stimuli. A typical sequence of trials is illustrated by the feedback messages given by the software (G = gain, L = loss). (B) Movement analysis. Trajectories and velocity profiles were reconstructed off-line from video recordings of performance. The example shows a trial with hesitation, characterized by a trajectory including one return to the keyboard, and by a profile containing multiple velocity peaks. The velocity profiles also served to determine the RT and MT.

tween On and Off states in PD-Dopa and PD-Stim groups.

Responses

PD patients tended to take longer to find the rules than control subjects, but this observed difference did not reach significance. For the control/PD-Dopa/PD-Stim groups, respectively, the total number of trials was 52.7/63.9/60.4 for all searching periods and 65.9/61.4/61.9 for all applying periods. Taking treatment into consideration, the number of trials was 58.7/71.1 and 59.1/63.7 for On/Off-Dopa and On/Off-Stim patients, respectively. This was the only parameter that was sensitive to the repetition effect [$F(1,51) = 19.9$, $p < .001$], indicating that discovery of rules got faster between the first and second assessments. There was no significant interaction between group and repetition, indicating that improvement across assessments was similar in the different groups.

The response score (percentage of correct responses) was only affected by uncertainty [$F(1,51) = 505.0$, $p < .001$]. All groups were roughly at chance level for the searching period (with scores of 46.0–48.6%), and almost perfect for the applying period (with scores of 97.0–98.6%). This drastic change of response scores clearly indicates the transition from uncertainty to knowledge about the rule.

Manual Performance

No factor was found to have a significant influence on the initiation rate (percentage of go movements initiated): this parameter was similar (between 52.4% and 59.3%), whatever the group, assessment, state, or period. Hence, all groups initiated a movement in approximately half of the trials, both when searching and when applying the rules.

The response time was divided into RT (between stimulus display and hand start) and MT (between hand start and screen touch). As with the response score, the RT was only affected by uncertainty [$F(1,51) = 138.9$, $p < .001$]. All groups took additional time to deliberate before initiating their movement in the searching period (RTs of 1.72–1.93 sec) compared with the applying period (RTs of 1.10–1.22 sec). The uncertainty effect is illustrated in Figure 2A by nonflat curves: In the course of the task, RTs increased at each searching period and decreased at each applying period.

The MT showed an effect of group [$F(2,51) = 6.8$, $p < .01$], in addition to uncertainty [$F(1,51) = 71.2$, $p < .001$], with an interaction between group and uncertainty [$F(2,51) = 25.8$, $p < .001$]. Each group was then tested for the motor slowing, defined as the difference from control subjects during the applying period, and for the uncertainty effect, defined as the difference between searching and applying periods. These post hoc comparisons allowed us to discriminate between three populations: firstly, control subjects and On-Dopa patients, with no motor slowing and no uncertainty effect (MTs of 0.81–0.84 sec whatever the period); secondly, On-Stim patients, with no motor slowing but an uncertainty effect (MTs of 1.18/0.78 sec for searching/applying periods); and thirdly, Off-Dopa and Off-Stim patients, with both a motor slowing and an uncertainty effect (MTs of 1.44–1.68/1.03–1.13 sec

Table 2. Comparison Between Applying and Searching Periods for the Main Experimental Variables

Group	*Control*	*PD-Dopa*		*PD-Stim*	
State	–	*OFF*	*ON*	*OFF*	*ON*
Score (%)					
Searching	46.0 ± 3.0*	46.3 ± 2.1*	48.6 ± 2.8*	47.4 ± 1.8*	48.2 ± 2.5*
Applying	98.6 ± 0.5	97.5 ± 0.6	97.6 ± 0.7	97.6 ± 0.6	97.0 ± 0.8
Initiation (%)					
Searching	58.7 ± 3.3	59.1 ± 3.1	56.3 ± 3.0	52.4 ± 3.5	59.3 ± 4.1
Applying	55.0 ± 1.2	56.3 ± 1.8	54.1 ± 1.5	54.2 ± 1.9	56.1 ± 1.5
Hesitation (%)					
Searching	8.5 ± 1.4	24.1 ± 2.5*	6.8 ± 1.3	20.7 ± 2.4*	22.5 ± 2.9*
Applying	7.4 ± 1.3	7.4 ± 1.6	5.9 ± 0.9	6.8 ± 1.0	6.7 ± 1.5
RT (sec)					
Searching	1.84 ± 0.13	1.72 ± 0.09	1.86 ± 0.15	1.93 ± 0.14	1.91 ± 0.12
Applying	1.10 ± 0.10	1.20 ± 0.09	1.12 ± 0.12	1.22 ± 0.12	1.20 ± 0.10
MT (sec)					
Searching	0.84 ± 0.06	1.44 ± 0.11*	0.81 ± 0.05	1.68 ± 0.16*	1.18 ± 0.12*
Applying	0.81 ± 0.05	1.03 ± 0.08	0.81 ± 0.06	1.13 ± 0.12	0.78 ± 0.06

Values are expressed as mean ± SEM. Response score and initiation rates (%) are expressed as the number of correct responses or initiated movements per 100 trials. For hesitations, the rate (%) is expressed as the number of observed hesitations per 100 initiated movements. RT = reaction time; MT = movement time.
*Searching period values that significantly differ from applying period values.

for searching/applying periods). These dissociations are illustrated in Figure 2A: The uncertainty effect is indicated by a nonflat curve mimicking that of RT, whereas motor slowing is indicated by the overall gap between curves corresponding to the On and Off states. Both L-Dopa and STN-DBS improved the motor slowing (with $p < .001$), but only L-Dopa corrected the uncertainty effect (with $p < .001$), not STN-DBS (with $p = .98$).

Correlations were systematically looked for between the uncertainty effect on MT, defined as MT(searching) minus MT(applying), and all other experimental, clinical, and demographic variables. The only correlated variable was the uncertainty effect on RT, defined as RT(searching) minus RT(applying). This correlation means that the more these patients deliberated, the more their movement was prolonged. It was only observed in Off-Dopa ($r = .73, p < .001$), Off-Stim ($r = .67, p < .01$), and On-Stim ($r = .70$, $p < .001$) patients, not in On-Dopa patients ($r = .04$, $p = .87$) or in control subjects ($r = -.29$, $p = .22$), as illustrated in Figure 2B.

This analysis of the uncertainty effect on movement execution revealed hesitations between go and no-go alternatives, mainly characterized by velocity profiles containing multiple peaks (Figure 3). Note that hesitations solely occurred in the searching period, and only in cases of DA depletion (Off-Dopa, On-Stim, and Off-Stim). These individual examples can be extended to groups (see Figure 4): In the course of the task, hesitations increased at each searching period and decreased at each applying period, except in the control and On-Dopa groups. Statistical results for the hesitation rate were very similar to those for MT, with an effect of group [$F(2,51) = 9.7, p < .01$], an effect of uncertainty [$F(1,51) = 106.3, p < .001$], and an interaction between group and uncertainty [$F(2,51) = 51.9, p < .001$]. Post hoc comparisons allowed us to discriminate between two populations: on the one hand, control subjects and On-Dopa patients, with rare hesitations whatever the period (rates of 5.9–8.5%), and on the other hand, On-Stim, Off-Stim, and Off-Dopa patients, with rare hesitations for applying periods (6.8–7.4%) but more frequent

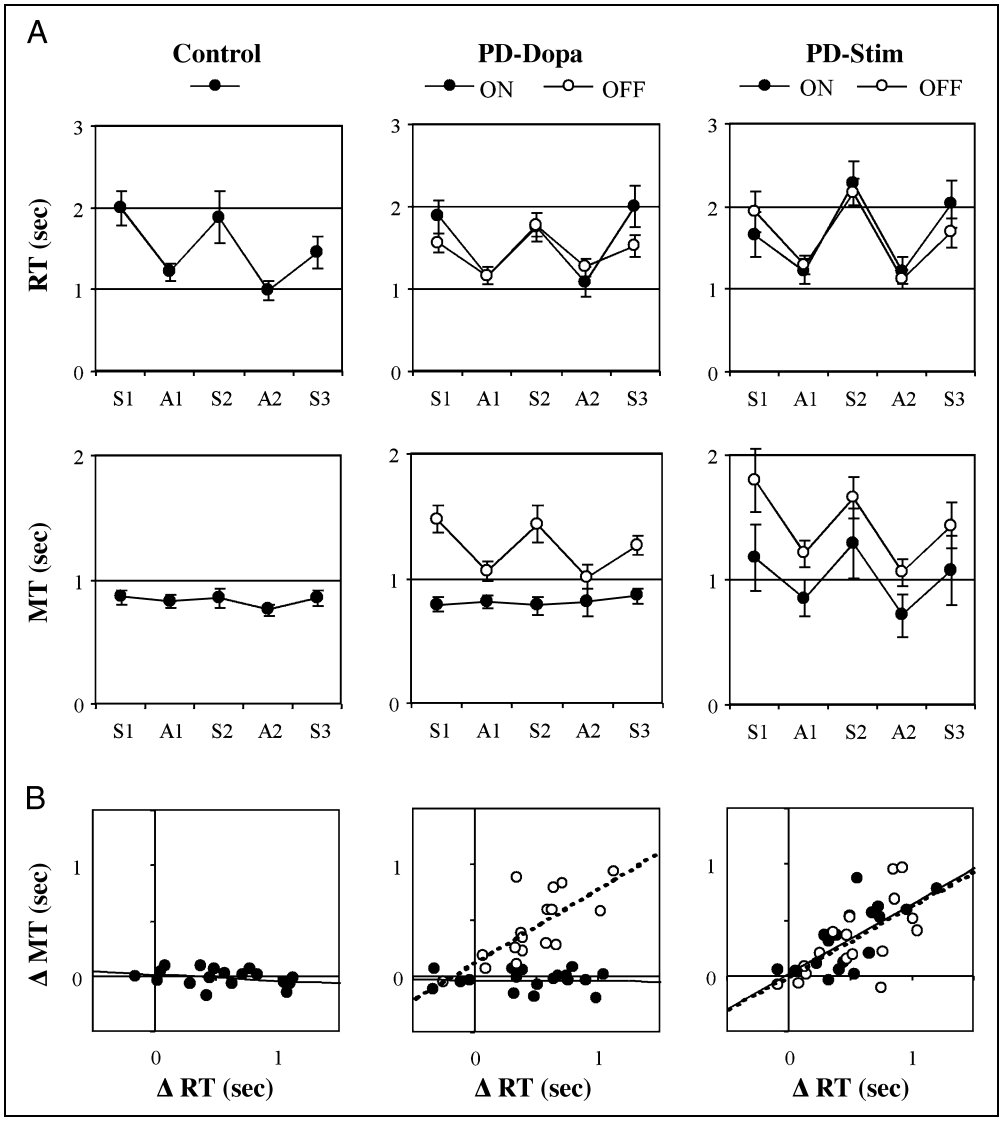

Figure 2. Reaction time (RT) and movement time (MT). (A) Evolution of RT and MT during task performance. Circles represent the mean and error bars the SEM. A = applying; S = searching; 1 = learning; 2 = reversal; 3 = extinction. (B) Correlation between the uncertainty effect on RT (ΔRT) and MT (ΔMT). Δ = T(searching) − T(applying). S1–3 data and A1–3 data were pooled to form the searching and applying periods, respectively. One circle represents the mean obtained by one subject. Not all subjects are visible because of superimposition. The dashed and full lines were obtained by linear regression of the OFF and ON distributions, respectively.

hesitations for searching periods (20.7–24.5%). The uncertainty effect on the hesitation rate was significantly corrected by L-Dopa (with $p < .001$) but not by STN-DBS (with $p = .27$).

DISCUSSION

The main effects of uncertainty were (1) in all groups of subjects: an additional time before the initiation of movement, revealing the engagement of mental deliberation; and (2) in the event of DA depletion: a prolonged and hesitating movement, revealing the temporal coupling of mental deliberation and motor execution.

At the Cognitive Level: A Loss of Uncoupling between Deliberation and Execution?

These effects are hard to compare with other published observations because, to our knowledge, manual performance of PD patients has not been studied in tasks involving decision under uncertainty. However, several deficits currently reported in the literature might explain the effect of uncertainty on movement execution: namely, motor disability, loss of motivation, and executive dysfunction.

A first possibility is that prolonged and hesitating movements merely result from motor disability. In this interpretation, movements would be more prone to hesitation in PD patients, because of the motor slowing associated with the pathology. However, in applying periods, the MT was not different between control subjects and patients treated either with L-Dopa or with STN-DBS. The motor slowing was therefore fully corrected by both treatments, whereas the uncertainty effect on movement was corrected by L-Dopa but not by STN-DBS. Thus, the correction of motor slowing can be dissociated from the correction of the uncertainty effect. Furthermore, no correlation was found between the uncertainty effect on MT and the UPDRS motor disability score.

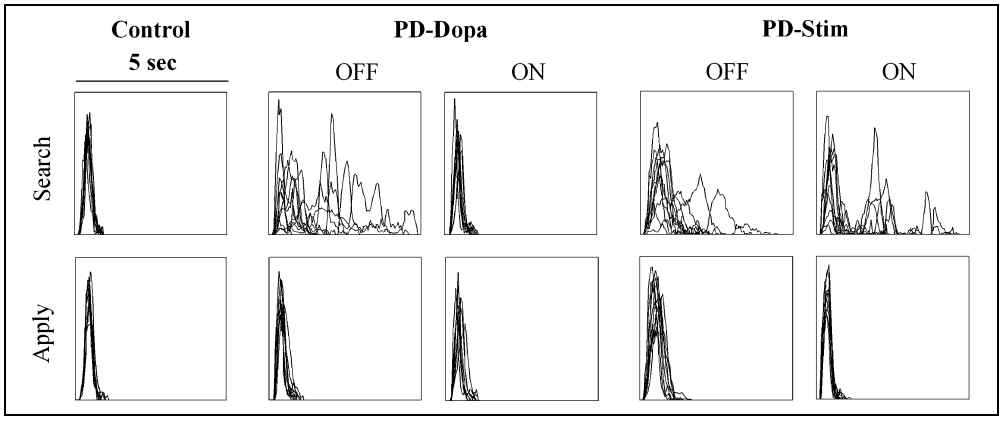

Figure 3. Examples of movement velocity profiles (arbitrary units). Each group is represented by one subject. The OFF and ON states correspond to the two assessments of the same patient. To preserve the visibility of the different curves, only the first 10 movements are used to illustrate each period.

A second possibility is that prolonged and hesitating movements result from apathy or depression, frequently observed in PD (Pluck & Brown, 2002; Aarsland et al., 1999; Starkstein et al., 1992), which may discourage the patients in periods of uncertainty. However, L-Dopa and STN-DBS have been shown to improve apathy equally, compared to the untreated state (Czernecki, Pillon, Houeto, Welter, et al., 2005; Funkiewiez et al., 2003). Moreover, there was no correlation between the response score on the depression scale (MADRS) and the uncertainty effect on MT in our study. The degree of motivation is also assessed by the number of trials needed to find out the rules, which was unchanged either with L-Dopa or STN-DBS. Moreover, there was no correlation between the number of trials and the uncertainty effect on MT. Thus, the correction of the uncertainty effect on movement by L-Dopa is unlikely to have been due to a higher degree of motivation.

A third possibility is that prolonged and hesitating movements result from executive dysfunction, a common characteristic of PD (Dubois & Pillon, 1997; Owen et al., 1992; Taylor, Saint-Cyr, & Lang, 1986). Difficulties in elaborating, maintaining, and modifying a set of responses could increase uncertainty for PD patients. However, there was no difference in the rate of correct responses between our groups of subjects, all groups being at chance level in periods of uncertainty. Also, a lack of mental flexibility could impair the inhibition of previously reinforced movements, hence, hesitations could merely be the late inhibition of incorrect movements. However, this would not explain why hesitations appeared as soon as the first searching period, when mental flexibility is not required. Lastly, hesitations could represent corrections of impulsive movements due to a discrete frontal impairment. However, there was no difference between groups either in RT or in initiation rate: PD patients were therefore not more impulsive than control subjects. Moreover, there was no correlation between the uncertainty effect on MT and the frontal score, calculated according to a previously published method (Pillon, Gouider-Khouja, et al., 1995). Furthermore, if prolonged MT was due to corrections following impulsive initiation of movement, it would be negatively correlated to RT. Yet the correlation was significantly positive in DA-depleted patients: The longer the deliberation, the longer the execution.

Thus, the effect of uncertainty on movement execution appears to be an independent and previously undescribed deficit in PD. In our view, the most convincing interpretation of such a deficit is that deliberation and execution are coupled in time, making the decision-related hesitations detectable in the gestures of patients.

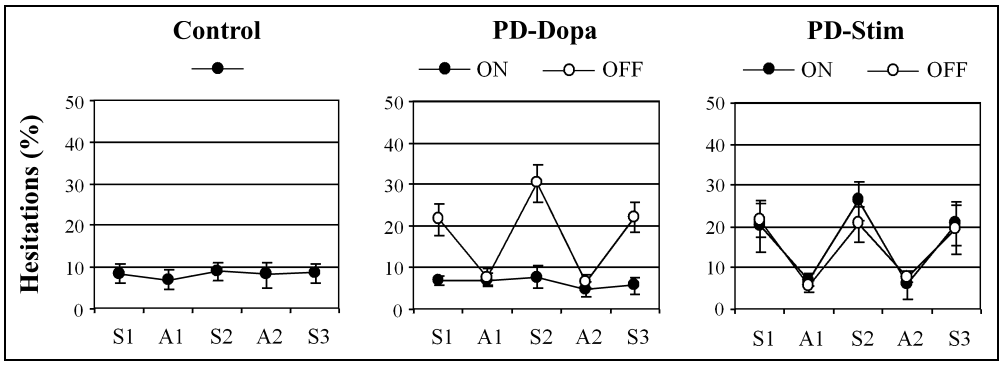

Figure 4. Frequency of hesitations. The frequency (%) is expressed as the number of hesitations per 100 initiated movements. Circles represent the mean and error bars the SEM. A = applying; S = searching; 1 = learning; 2 = reversal; 3 = extinction.

At the Neuronal Level: A Loss of Uncoupling between Basal Ganglia Circuits?

The loss of uncoupling between deliberation and execution offers a neat dissociation between antiparkinsonian treatments, because it is reversed by L-Dopa but not by STN-DBS. A pathophysiological interpretation must therefore involve specific effects of L-Dopa on neuronal circuits.

A first possibility is that L-Dopa and STN-DBS do not affect the same neuronal circuits. One might assume that L-Dopa would influence both motor and nonmotor circuits, whereas STN-DBS would only affect the motor circuit. However, axonal tracing studies in monkeys have delineated nonmotor areas within the STN (Kelly & Strick, 2004; Joel & Weiner, 1997), and brain imaging studies in PD patients have reported metabolic changes in nonmotor frontal areas under STN-DBS (Hilker et al., 2004; Limousin et al., 1997). Moreover, comparisons between the On and Off states have shown that L-Dopa and STN-DBS similarly improve nonmotor functions (Jahanshahi et al., 2000; Pillon, Ardouin, et al., 2000).

In other respects, although both treatments are known to influence the BG, only L-Dopa is thought to act directly on the frontal cortex. However, we previously observed movements resembling hesitations in monkeys with MPTP-induced DA depletion (Pessiglione, Guehl, Hirsch, et al., 2004). As they were particularly frequent during performance of tasks involving both motor and cognitive difficulties, the monkeys' apparent hesitations can also be interpreted as resulting from interference between motor and cognitive processes. These hesitations were observed before the appearance of gross motor symptoms, when degeneration was restricted to the nigrostriatal dopaminergic pathway, relatively sparing the mesocortical dopaminergic pathway (Pessiglione, Guehl, Jan, et al., 2004). Thus the DA-related uncoupling of deliberation and execution may occur within the BG rather than the frontal cortex.

A second possibility is that L-Dopa and STN-DBS affect information processing differently within the BG. In physiological conditions, the striatum receives phasic and widespread waves of DA in response to a stimulus that predicts a coming reward, or to the reward itself if unexpected (Schultz, Dayan, & Montague, 1997). The DA-mediated reinforcement signal is likely to modify the strength of corticostriatal synapses that lead to adapted behavior (Calabresi et al., 2000; Wickens, Begg, & Arbuthnott, 1996). Thus, the lack of DA signal may impair reinforcement learning, which could explain the difficulty of PD patients in learning and reversing stimulus–response associations, as reported in some (Czernecki, Pillon, Houeto, Pochon, et al., 2002), but not all (Swainson et al., 2000), studies. The impaired reinforcement of stimulus–response associations may then impede the selection of the adapted action, as previously described in MPTP-treated monkeys (Pessiglione, Guehl, Agid, et al., 2003). Indeed, a hesitation can be interpreted as a dysfunctional selection: The desired action is insufficiently activated and the other is insufficiently inhibited. However, a pure deficit in action selection would have been observed in applying periods as well as in searching periods. Moreover, L-Dopa has been shown to leave unaffected or even to worsen stimulus–response learning, reversal, and extinction (Czernecki, Pillon, Houeto, Pochon, et al., 2002; Cools et al., 2001; Swainson et al., 2000). Thus, the tonic effect of L-Dopa cannot replace the reinforcement signal carried by the phasic DA release, whereas it is able to restore the uncoupling of deliberation and execution.

In contrast, the tonic effect of L-Dopa is likely to restore the functional segregation between BG circuits. MPTP-induced DA depletion impairs the focusing of cortico-striato-pallidal synaptic transmission, so that a given pallidal neuron can respond to distant striatal sites of microstimulation (even when one is in the caudate nucleus and the other is in the putamen), and a given striatal site of microstimulation can induce responses from distant pallidal neurons (Tremblay, Filion, & Bedard, 1989; Filion, Tremblay, & Bedard, 1988). The pallidal responses to striatal stimulation were normalized by systemic injection of apomorphine (a nonspecific DA agonist). The loss of information focusing is also thought to result in an abnormal correlation between the activities of pallidal neurons (at a distance of up to 5 mm), which was induced by MPTP intoxication and reversed by DA replacement therapy (Heimer, Bar-Gad, Goldberg, & Bergman, 2002; Raz, Vaadia, & Bergman, 2000; Nini, Feingold, Slovin, & Bergman, 1995). These results have been replicated in PD patients (Hurtado, Gray, Tamas, & Sigvardt, 1999), including the desynchronization effect of dopaminergic treatment (Brown et al., 2001; Levy et al., 2001). Moreover, a loss of information focusing has also been found in efferent structures of the BG, such as the ventral anterior and lateral thalamic nucleus (Pessiglione, Guehl, Rolland, et al., 2005), the premotor cortex (Goldberg et al., 2002), and the supplementary motor area (Escola et al., 2002). Furthermore, magnetoencephalographic studies have revealed abnormal coupling between distinct frontal areas, such as the anterior cingulate and primary motor cortices, in untreated PD patients (Timmermann et al., 2003). Such abnormal coupling is unlikely to be reversed by STN-DBS, which consists of widespread high-frequency pulses, considered to reduce firing rate and/or regularize firing patterns in the output structures of the BG (Hashimoto, Elder, Okun, Patrick, & Vitek, 2003; Lozano, Dostrovsky, Chen, & Ashby, 2002; Benazzouz & Hallett, 2000). Thus, the loss of uncoupling between BG circuits, which is likely to be reversed by L-Dopa but not by STN-DBS, represents a suitable pathophysiological mechanism to explain the loss of uncoupling between deliberation and execution.

Conclusion

In untreated PD patients, we found a disruption of movement execution in a situation requiring decision-making in uncertainty, which was corrected by L-Dopa but not by STN-DBS. At a cognitive level, this disruption may be due to a loss of temporal uncoupling between mental deliberation and motor execution, leading to decision-related hesitations being expressed as movements. At a neuronal level, this disruption may be due to a loss of functional segregation between BG circuits. Interference between functional circuits or subcircuits could also explain certain sensorimotor deficits observed in PD (Low, Miller, & Vierck, 2002; Praamstra & Plat, 2001). For example, it could explain why PD patients are particularly impaired in the performance of simultaneous movements (Castiello, Stelmach, & Lieberman, 1993; Benecke, Rothwell, Dick, Day, & Marsden, 1986) or double-task paradigms (Malapani, Pillon, Dubois, & Agid, 1994; Brown & Marsden, 1991).

Interestingly, the loss of uncoupling between deliberation and execution, observed in the DA-depleted brain, raises questions about the functioning of the healthy brain. A first question is how exactly the uncoupling is achieved. In particular, one may wonder if the normal brain stops deliberation when execution is engaged, or processes deliberation and execution in parallel without interference. A second question is whether coupling represents a strategy available to the normal brain. One can speculate that decreasing the DA level would allow an action to be performed under attentional control, and increasing the DA level would allow an action to be performed without being perturbed by the ongoing thought. Accordingly, healthy chess players would be able to adopt both coupling and uncoupling strategies, whereas unmedicated PD chess players would inevitably let their hesitations appear in their gestures.

METHODS

Subjects

The study was approved by the Ethics Committee for Biomedical Research of the Salpêtrière Hospital. The subjects did not receive any form of reward for their participation. Three groups of 18 subjects were included in the study: healthy subjects (''control'' group), PD patients without electrode implantation (''PD-Dopa'' group), and PD patients with electrode implantation (''PD-Stim'' group). PD-Dopa patients were consecutively hospitalized as candidates for surgery, and PD-Stim patients for therapeutic follow-up, on average, 18.5 months after surgery. Surgery consisted of bilateral implantation of quadripolar electrodes in the STN. Stimulation materials (Medtronic, Minneapolis, MN) and methods (surgical targeting, adjustment of DBS parameters) have been detailed elsewhere (Bejjani et al., 2000). Inclusion criteria for patients were: idiopathic PD with a good response to L-Dopa (>40% improvement on the Unified Parkinson's Disease Rating Scale [UPDRS]), absence of depression (score <20 on the Montgomery and Asberg Depression Rating Scale [MADRS]), and absence of dementia (score >130 on the Mattis Dementia Rating Scale [Mattis DRS]). Additional assessment comprised a frontal score including the Wisconsin Card Sorting Test (Pillon, Gouider-Khouja, et al., 1995), and a verbal learning test (Grober, Buschke, Crystal, Bang, & Dresner, 1988). All available data relative to demographic characteristics (age, sex, and education level), motor disability (disease duration and UPDRS score), and neuropsychological assessment (MADRS score, Mattis DRS score, Pillon frontal score, and Grober free recall) were compared between the two PD groups using a Student's t test: No significant differences were found. Control subjects were selected to match patients for age, sex, and level of education, and were also assessed on the MADRS and Mattis DRS (Table 1). All these data were then compared with a global ANOVA taking the three groups into consideration: Significant differences were only found for the MADRS [$F(2,51) = 6.4$, $p < 0.01$] and the Mattis DRS [$F(2,51) = 6.4$, $p < .05$] scores.

Experimental Procedure

Each group of subjects was assessed twice on the go/no-go task described below. Due to medical constraints, the interval between the two assessments varied from 2 to 24 hours (on average 13/19/24 hours for the PD-Stim/PD-Dopa/control groups, respectively). Each PD group was randomly divided into two subgroups of nine subjects each, one subgroup being assessed first in the ''On'' state and second in the ''Off'' state, and the other in reverse order. For the PD-Dopa group, ''On'' means at maximal therapeutic effect of dopaminergic treatment, and ''Off'' means after at least 12 hours of therapeutic withdrawal. For the PD-Stim group, ''On'' means at maximal therapeutic effect of STN-DBS, and ''Off'' means at least one hour after STN-DBS had been stopped. In both cases, PD-Stim patients were deprived of dopaminergic treatment for at least 12 hours prior to assessment. Thus, the Off states allow untreated patients to be assessed, whereas the On states allow the two treatments to be compared.

The go/no-go task used in the present study was adapted from the reversal/extinction task proposed by Rolls, Hornak, Wade, and McGrath (1994). Briefly, two highly discriminable fractal images are displayed one at a time with equal frequency on a computer screen (see Figure 1), following a pseudorandom order. Subjects can advance to each new trial at their own pace by pressing the space bar of the keyboard. They are informed that the task consists of deciding whether or not to touch the stimulus, within a 7-sec delay. The screen is touch-sensitive and allows the subjects' responses to be de-

tected and recorded. If the screen is touched, the stimulus is immediately replaced by a feedback message, indicating whether a point has been gained or lost. If the screen is not touched, the message appears after the 7-sec delay. A running total of the points obtained (starting from 0) is continuously displayed at the top of the screen. Subjects are asked to try to gain as many points as possible.

At the beginning of the task, an implicit learning rule specifies the value (''go'' or ''no-go'') of each stimulus (see Figure 1A). One point is gained when touching the go stimulus or not touching the no-go stimulus, otherwise one point is lost. In the absence of any indication, subjects must search for the rule with a trial-and-error approach. The rule is considered to have been correctly applied when subjects make at least nine point-gaining responses in 10 consecutive trials. This last series of trials is called the ''applying period,'' as opposed to the ''searching period,'' which includes all preceding trials. Once the applying period is over, the software automatically changes the rule without warning. The first change is a reversal (the go stimulus becomes the no-go stimulus and vice versa), whereas the second change is an extinction (both stimuli take the no-go value). Thus, three searching and three applying periods can be studied in one assessment, corresponding to the three successive rules (learning, reversal, extinction). However, the last period was not included in the movement analysis, as applying the extinction rule consists of making no movement. For each searching period, the analysis was limited to the 30 trials preceding the next applying period. For each applying period, the analysis comprised 10 or 11 trials, the last one resulting in the first point lost because of rule change. With this procedure, the number of trials was approximately balanced between searching and applying periods (see Results).

Data Analysis

Subjects' responses were recorded on-line by the task-related software, allowing the number of trials and a response score to be calculated for the different periods. The response score is the percentage of correct responses (namely, touching a go or not touching a no-go stimulus). Subjects' manual performance was recorded on video tape and rated off-line using image analysis software (Viewpoint, Lyon, France), as previously described (Pessiglione, Guehl, Agid, et al., 2003). All trials ending with a touch response, whether correct or not, were included in this video analysis. Firstly, the trajectories of movements from the keyboard to the screen were reconstructed using ''Synchrotracker'' software (Viewpoint). The tracing of trajectories served to identify reaching movements that transiently returned to the keyboard. Secondly, the velocity profiles of reaching movements were reconstructed using the ''Vigie Primates'' software (Viewpoint). The window of analysis was positioned between the keyboard and the screen to detect hand movements. The recordings allowed the RT (between stimulus display and first hand move) and MT (between first hand move and stimulus extinction) to be calculated. These recordings also served to calculate the initiation and hesitation rates. Initiation rate is the percentage of trials when the hand enters the window detecting movements directed towards the screen. Hesitation rate is the percentage of reaching movements that includes at least one turning back on the trajectory and two peaks on the velocity profile.

The same statistical procedure was carried out for all collected parameters (number of trials, response score, initiation and hesitation rates, RT, and MT). A global ANOVA was performed with the group (control, PD-Dopa, PD-Stim) as a between factor, and repetition (first vs. second assessment) and uncertainty (searching vs. applying period) as within factors. Data from the two assessments were pooled (Table 2) for all the parameters that were not sensitive either to repetition effect, interaction between repetition and group, or interaction between repetition and uncertainty. For parameters showing a significant interaction between uncertainty (searching vs. applying period), group (PD-Dopa vs. PD-Stim), and state (On vs. Off), post hoc Tukey's test was then used to compare the uncertainty effect between all subgroups (control, Off-Dopa, On-Dopa, Off-Stim, On-Stim) and between On and Off states in PD-Dopa and PD-Stim groups. Correlations between uncertainty-sensitive parameters and demographic or clinical variables were looked for using the nullity test of Pearson's coefficient. The significance threshold was set at $p < .05$, taking into account Bonferroni corrections relative to the number of tests performed.

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