Pharmacologically modulated fMRI—cortical responsiveness to levodopa in drug-naive hemiparkinsonian patients

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Summary

According to the basal ganglia–thalamocortical circuit model, dopamine depletion in the nigrostriatal system leads to hypoactivation in the supplementary motor area (SMA) and the primary motor cortex (M1) in Parkinson’s disease. This functional cortical deafferentation and its reversibility by levodopa (L-dopa) treatment has been established in previous studies for SMA but remains controversial for M1. We used functional MRI (fMRI) and a simple finger opposition task to correlate blood oxygenation level-dependent (BOLD) signal changes with motor performance, assessed separately for each hand between fMRI scanning sessions. Eight drug-naive patients with an akinetic idiopathic hemiparkinsonian syndrome (Hoehn and Yahr stage 1–1.5) and 10 healthy controls were studied. Patients performed a simple, auditory-paced random finger-opposition task every 3 s before and repeatedly every 20 min after intake of 300 mg of fast-release L-dopa. M1 contralateral to the affected hand and SMA, predominantly of the contralateral side, showed a BOLD signal increase after L-dopa intake. Furthermore, comparing BOLD responses of M1 and SMA between the patients and controls revealed that these areas were hypoactive before L-dopa treatment. Signal changes in M1 and SMA were highly correlated with motor performance, which increased after L-dopa intake. This result is not confounded by a performance effect because the motor task employed during scanning was identical throughout all sessions. In contrast to previous imaging studies in which cortical reorganization in Parkinson’s disease was thought to have caused M1 hyperactivation, our data are in accordance with the hypothesis that, in de novo idiopathic hemiparkinsonian syndrome, motor cortex hypoactivation in contralateral M1 and bilateral SMA is caused by a decreased input from the subcortical motor loop, which is reversible by L-dopa.

Keywords: fMRI; Parkinson’s disease; levodopa; BOLD; motor cortex

Abbreviations: BgT = basal ganglia–thalamocortical circuit; BOLD = blood oxygenation level-dependent; fMRI = functional MRI; L-dopa = levodopa; M1 = primary motor cortex; PMC = premotor cortex; rCBF = regional cerebral blood flow; SMA = supplementary motor area; SPM = statistical parametric map

Introduction

Idiopathic Parkinson’s disease is characterized by hypokinesia due to degeneration of the nigrostriatal dopaminergic system. According to the basal ganglia–thalamocortical circuit (BgT) model (Alexander et al., 1990), dopamine depletion leads to reduced excitatory thalamic outflow to the frontal lobe. The BgT circuits are organized in a parallel manner with structural and functional segregation from each other (Alexander et al., 1986) and with separated thalamocortical frontal projections. In non-human primates the hand/arm motor area and adjacent premotor area receive strong superficial basal ganglia–thalamocortical projections (Nakano, 2000). Hypokinesia in Parkinson’s disease is believed to be a result of dopamine deficiency in the ‘motor circuit’, comprising the supplementary motor area (SMA), parts of the premotor cortex (PMC) and the primary motor cortex (M1) (Alexander et al., 1990). This hypothesis of functional cortical deafferentation is supported by brain imaging studies showing diminished regional cerebral blood flow (rCBF) in the SMA (Jenkins et al., 1992; Playford et al., 1992; Rascol et al., 1992, 1994; Samuel et al., 1997), the
prefrontal cortex (Playford et al., 1992) and M1 (Rascol et al., 1992) in Parkinson’s disease patients. Reduced activity in the SMA was shown to be partly reversible by dopaminergic treatment (Jenkins et al., 1992). Recent functional MRI (fMRI) studies of motor performance in Parkinson’s disease patients (Sabatini et al., 2000; Haslinger et al., 2001) are only partially in accordance with the hypothesis described above. Hypoactivity of rostral SMA was confirmed, but hyperactivity (Sabatini et al., 2000) as well as hypoactivity (Haslinger et al., 2001) was found in the caudal part of the SMA. More importantly, in contrast with the BgT circuit model, hyperactivity was found bilaterally in M1 and the lateral PMC (Sabatini et al., 2000). Additionally, an increase in activity in the SMA and a decrease in M1 and the lateral PMC after L-dopa intake has been reported (Haslinger et al., 2001). This unexpected hyperactivity in M1 was interpreted as a result of reorganization of an impaired motor system. According to this hypothesis, M1 would compensate for an impaired subcortical motor system. M1 hyperactivity might also be related to pretreatment of patients with dopaminergic drugs. This hypothesis is supported by studies in patients with moderate L-dopa-associated dyskinesia that describe M1 and PMC hyperactivity (Brooks et al., 2000; Rascol et al., 1998).

To avoid these potential confounds and to assess the pathophysiology of the disease before potential reorganization can occur, we studied untreated early-stage patients with idiopathic hemiparkinson syndrome [stage 1–1.5 (Hoehn and Yahr, 1967)], using fMRI. In hemiparkinson patients, the less affected hemisphere can serve as an intra-individual control. However, it is known that the nigrostriatal system contralateral to the clinically unaffected hand in hemiparkinsonian patients is already affected at the early stages (Brooks, 1991). fMRI provides high spatial resolution and the possibility of sequential scanning without risk for the patient. We employed a very simple random finger movement task in the scanner to investigate the activation pattern of the ‘motor circuit’ in M1, SMA and PMC and we correlated BOLD signal changes with motor performance. In accordance with the BgT circuit model, we hypothesized functional cortical deafferentation of motor areas in de novo Parkinson’s disease patients before L-dopa treatment. Furthermore, we expected an increase in activation caused by L-dopa in these areas, reflecting normalization of the activity of these parallel pathways of the motor circuit (Alexander et al., 1990). To further clarify whether M1 and SMA are hypoactive or hyperactive in drug-naive Parkinson’s disease patients, we studied an age-matched control group.

**Material and methods**

**Parkinson’s disease patients**

Eight drug-naive patients [seven male, one female, age 54 ± 12 years (mean ± SD), disease duration 13 ± 6 months (mean ± SD)] with akinetic idiopathic hemiparkinson [stage 1–1.5 (Hoehn and Yahr, 1967)] syndrome according to the diagnostic criteria of the UK Parkinson’s Disease Society Brain Bank (Gibb and Lees, 1988) were studied. Three subjects were left-handed and five subjects right-handed. None of them had ever had a dopaminergic or other Parkinson-related drug treatment. In all patients, tremor was almost undetectable. Patients were not suffering from any other neurological or psychiatric disorder. Every patient was pretreated with domperidone (Motilium™), 3 × 10 mg daily on each of the 3 days before examination, in order to prevent nausea. After each scanning session, once before and five times after L-dopa intake, hand motor performance was tested according to parts of the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS). We assessed rapid alternating hand movements with pronation and supination and finger taps in rapid succession, using thumb-to-index finger opposition with the widest amplitude possible. The number of movements within 20 s was counted separately for each hand by two investigators. In each patient the most sensitive parameter was taken to be L-dopa-influenced motor performance measured outside the scanner.

**Control group**

We studied 10 healthy, age-matched control subjects (seven female, three male, mean age 57 ± 9 years). Control subjects were all right-handed.

Written informed consent was obtained from all patients and controls prior to examination and the study was approved by the Local Ethics Committee of Hamburg.

**Task and paradigm**

In the scanner, patients and controls performed a simple, auditory-paced random finger-opposition task (thumb to digit) every 3 s (0.3 Hz). They were advised to select a finger at random and to avoid repetitions and fixed sequences. This task was performed 10 times for each hand, with 30 s rest between hands (i.e. rest, left, rest, right, rest, …). Before measurements were made, the patients were trained to keep the amplitude, acceleration and the thumb-to-finger pressure of the simple motor task constant. Amplitude and pressure were categorized in three levels (1–3) and patients were told to keep to a medium level (level 2). In one patient, we additionally measured the pressure between the thumb and other fingers using a force transducer system. Six sessions with 120 scans each were performed every 15–20 min up to 120 min. One session was performed before and five sessions after intake of 300 mg fast-release L-dopa (Madopar LT™) orally. After each session, maximal motor performance was assessed. Blood was taken for measurement of the plasma level of L-dopa before the next scanning session started (Fig. 1). During blood sampling and motor performance assessment, the patient remained on the scanner bed but was moved out of the magnet. The control subjects were only investigated without L-dopa.
MRI scanning was performed on a 1.5 T scanner (Siemens Vision, Erlangen, Germany). Subjects wore headphones, which presented an 0.3 Hz auditory pacing signal; the headphones were connected to and driven by (via a plastic tube) a computer outside the magnet room. The head was fixed by foam pads in a standard head coil. Subjects were told to keep their eyes closed during image acquisition. One hundred and twenty volumes with 26 contiguous, axial, 3 mm thick slices (1 mm gap) were acquired per session using a gradient echo echo-planar imaging (EPI) T2*-weighted sequence (repetition time 2800 ms, echo time 60 ms, flip angle 90°, matrix 64×64, field of view 210×210 mm). Six sessions with a total of 720 volumes were carried out. The slices were oriented to cover the frontal, parietal and temporal cortices. A high-resolution (1×1×1 mm voxel size) structural MRI was acquired for each volunteer using a standard 3D T1-weighted fast low-angle shot (FLASH) sequence.

Image processing and statistical analysis
Image processing and statistical analysis were carried out using SPM99 (Friston et al., 1995a; Worsley and Friston, 1995). The first five scans of each session were discounted to avoid magnetic saturation effects. All volumes were realigned to the first volume, motion-corrected, spatially normalized (Friston et al., 1995b) to a standard EPI template (Talairach and Tournoux, 1988; Evans et al., 1994) and finally smoothed using a 6 mm full-width at half-maximum isotropic Gaussian kernel.

Data analysis was performed by modelling finger movements as trains of delta functions convolved with a hemodynamic response function. Regression coefficients (parameter estimates) for all regressors were estimated using least-squares within SPM99 (Friston et al., 1995c).

Specific effects were tested with appropriate linear contrasts of the parameter estimates for the regressor of both trial types, resulting in a t-statistic for each and every voxel. These t-statistics constitute a statistical parametric map (SPM). SPMs are interpreted by referring to the probabilistic behaviour of Gaussian random fields. Data were analysed for each subject individually and for the group.

For the display of data for single subjects, the high-resolution structural MRI of each subject was co-registered to the functional scans by normalizing it to a T1-weighted template in the same space as the template used to normalize the functional data set.

Single-subject and group analyses were performed. For the group analysis, the hemispheres of three patients were mirrored (‘flipped’) digitally to achieve a comparable group image of all hemiparkinsonian patients affected at the same body side.

The two cerebral hemispheres are not strictly symmetrical, so that flipping introduces additional spatial noise. This effect is weakened by spatial smoothing, as used in our analysis. It is also important to note that, by using flipped data, it was possible to include Parkinson’s disease subjects who were
affected on their dominant arm and those who were affected on their non-dominant arm. We therefore avoided the bias of hand-dominance, which occurs if one only studies Parkinson’s disease patients affected in only the right or left arm.

Finally, we compared the activation level of patients before L-dopa intake with that of healthy controls, to make inferences about the level of activation in the motor system of the Parkinson’s disease patients relative to the control group.

Results

Plasma level of levodopa

After L-dopa intake, none of the patients showed side-effects, such as vomiting, hypotension or somnolence. The plasma levels of L-dopa were sufficient and temporally related to drug intake in all patients, although with major differences in peak plasma levels (Fig. 2).

Metabolism of L-dopa was normal and in all patients the 3-O-methyldopa (3-OMD) level was low, indicating that the subjects had not received previous L-dopa medication. Single-subject analyses showed that the peak L-dopa plasma level occurred on average 37.4 ± 16 min (mean ± SD) after L-dopa intake and 25 ± 18 min (mean ± SD) before the highest motor performance was reached. In every subject motor performance improvement was delayed with respect to the increase in L-dopa plasma level. Despite the decrease in L-dopa plasma level after the peak, motor performance remained at a high level for at least 120 min.

Task performance

Visual inspection confirmed that all patients performed the simple auditory-paced motor task in the scanner with a constant frequency during all sessions. L-Dopa treatment did not change movement velocity. In one subject we also measured thumb-to-digit pressure during movements using a force transducer, and found no systematic difference between sessions. Before L-dopa intake, motor performance (measured outside the scanner) of the affected side was lower than that of the clinically unaffected side in all patients (mean −19.5 ± 9.2%). After L-dopa intake, motor performance increased in all subjects on the affected side and reached the same level as in the contralateral hand (mean −3.4 ± 7.8%). The performance increase of the affected hand was much steeper than that of the clinically unaffected side, for which performance showed a more or less fluctuating curve, with little increase in some patients (Fig. 3).

Neuroimaging

When the two hemispheres were compared in the group analysis before L-dopa intake (Fig. 4), M1 contralateral to the affected hand (Fig. 4B) revealed significantly fewer activated voxels during performance of the simple auditory-paced motor task than M1 contralateral to the unaffected hand (Fig. 4A). This difference in activated voxels was found at very low (P < 0.05 uncorrected), intermediate (P < 0.001 uncorrected) and high (P < 0.05 corrected) thresholds (Fig. 4). However, comparing the BOLD signal level of each peak directly did not reveal a significant difference in peak height.

When BOLD signal levels were compared before and after 45 min after L-dopa intake (Fig. 5), the M1 contralateral to the affected hand (x = −39, y = −24, z = 51 mm, Z = 5.5) and bilateral SMA (x = −3, y = −6, z = 57 mm, Z = 5.6), predominantly of the contralateral side, showed an increase in BOLD signal (P < 0.05 corrected for SMA and M1 contralateral and P < 0.001 uncorrected for SMA ipsilateral) (Fig. 5A). The same M1 also showed a distinct increase when moving the unaffected (ipsilateral) hand (Fig. 5B). M1 contralateral to the unaffected hand showed a nearly constant response (Fig. 5B, no BOLD increase), in accordance with no major change in motor performance.

Correlation of BOLD activity with increase in motor performance (measured outside the scanner) (Fig. 1) was found in SMA (x = 0, y = −9, z = 57 mm, Z = 4.7) and M1 (x = −33, y = −27, z = 54 mm, Z = 6.7) contralateral to the affected hand (Fig. 6A). Bilateral SMA showed a weaker but marked performance-correlated increase (contralateral M1, P < 0.01 corrected; bilateral SMA, P < 0.001 uncorrected), M1 contralateral to the clinically unaffected hand also showed a small performance-correlated BOLD effect (P < 0.01 corrected) but in a more apical region compared with the affected side (Fig. 6B). Correlation between motor performance and activation (Fig. 7) was high (>0.7) in eight out of eight subjects in M1 (Fig. 7A), and slightly noisier in SMA (only five out of eight patients showed a correlation coefficient >0.7) (Fig. 7B).
Control group
The comparison of BOLD signal changes related to movement of the right hand (affected side in the patients) between healthy controls and Parkinson’s disease patients showed a significant ($P < 0.05$ corrected for small volume; sphere of radius 10 mm) difference in the M1 ($x = -45$, $y = -21$, $z = 54$ mm, $Z = 3.3$) and in the SMA ($x = -6$, $y = -18$, $z = 51$ mm, $Z = 3.8$). Overlaying this result onto the SPM obtained from the analysis in which BOLD signal changes were correlated with performance revealed overlap in M1 and SMA, showing that these areas are hypoactive in relation to healthy controls (Fig. 8).

Discussion
We have shown that, in early untreated (de novo) hemiparkinsonian patients, bilateral SMA and M1 contralateral to the clinically affected hand show less activation compared with the unaffected side when a simple motor task is performed. Intake of L-dopa intake leads to an increase in activation in these areas, which suggests underactivation in untreated Parkinson’s disease patients.

According to the BgT model, we expected functional deafferentation in the cortical motor area in Parkinson’s disease as a result of diminished transthalamic cortical input (Alexander et al., 1990), which should be normalized by
Correlation of BOLD signal with motor performance (the latter assessed between fMRI sessions) was found in M1 contralateral to the affected hand and to a lesser but still marked extent in bilateral SMA (A). M1 contralateral to the clinically unaffected hand also showed a small performance-correlated BOLD effect, but it was more apical than on the other side (B).

Forty-five minutes after l-dopa intake, the primary motor cortex (M1) contralateral to the affected hand and supplementary motor areas (SMA), predominantly of the contralateral side, showed an increase in BOLD signal (A). The same M1 also showed a distinct increase when moving the unaffected (ipsilateral) hand (B). In contrast, no increase in BOLD signal was seen in M1 contralateral when moving the unaffected hand.

Correlation of BOLD signal with motor performance (the latter assessed between fMRI sessions) was found in M1 contralateral to the affected hand and to a lesser but still marked extent in bilateral SMA (A). M1 contralateral to the clinically unaffected hand also showed a small performance-correlated BOLD effect, but it was more apical than on the other side (B).
dopaminergic treatment. From studies in non-human primates, the hand/arm motor area and adjacent premotor area are known to receive strong basal ganglia–thalamocortical projections (Nakano, 2000) as the target for the motor circuit.

Concerning SMA, our data are in line with the BgT model and previous brain imaging studies (Jenkins et al., 1992; Playford et al., 1992; Rascol et al., 1992, 1994; Samuel et al., 1997). Regarding M1, our results are also in accordance with the BgT model, but only partly in line with previous PET, single photon emission computed tomography (SPECT) and fMRI investigations (Rascol et al., 1992, 1998; Samuel et al., 1997; Brooks et al., 2000; Sabatini et al., 2000; Haslinger et al., 2001).

In contrast to other studies, we not only compared Parkinson’s disease patients with healthy controls but also investigated hemiparkinsonian patients, in whom the hemisphere contralateral to the clinically affected body side can serve as an approximate control for the affected side. Although it is known that even in hemiparkinsonian patients both sides of the basal ganglia are affected, this intrinsic control allows comparison within subjects. Furthermore, within-subject comparisons are unaffected by the gross motivational factors that can be observed when comparing patients with healthy controls.

**Motor cortex activity before levodopa intake**

Before L-dopa intake in hemiparkinsonian patients, M1 contralateral to the clinically affected body side is less activated than M1 contralateral to the unaffected side. This concerns the volume of activity and is maintained regardless of the threshold chosen. Insofar as the subjects were performing the simple motor task identically with both hands, the result is in agreement with the hypothesis of more severely diminished thalamocortical activation in the more affected hemisphere in hemiparkinsonian patients. It is possible that this finding simply reflects the recruitment of more muscle groups as the dopamine deficit is reduced.

**Plasma levels of L-dopa and motor performance**

We measured plasma levels of L-dopa and 3-OMD after each scanning session. Therefore we could confirm the quantity and kinetics of reabsorption. The 3-OMD data confirmed that patients had not received L-dopa previously and that they metabolized L-dopa normally.

After the plasma peak of L-dopa, motor performance remained high compared with baseline. This could have been expected on the basis of the relatively intact dopamine storage capacity of the striatum in early stages of Parkinson’s disease.
disease (Brooks, 2000), in which the clinical effect of L-dopa lasts longer than would be expected from the short half-life of L-dopa.

Primary motor cortex activation before and after L-dopa intake

As predicted by the BgT model, we found hypoactivity in M1 contralateral to the affected hand in untreated de novo hemiparkinsonian patients. This suggests functional deafferentation of the symptomatic side. Another main finding is the cortical activation increase in M1 contralateral to the affected hand after L-dopa intake. According to the simple finger opposition motor task in the scanner, this increase was limited to the hand area of M1, indicated by the omega (Ω) shape of the precentral gyrus at this location (‘hand knob’) (Yousry et al., 1997). Furthermore, this increase was found at the same location as the main effect of hand movement irrespective of L-dopa intake.

Even though we used simple paced finger movements, there is the possibility that improved performance during the task is responsible for the increase of activation in M1 and SMA over time. In particular, earlier movement onset after L-dopa treatment could be expected. However, in contrast to an event-related design, a block design, as employed in our study, is robust with respect to treatment-related shifts in movement onset. Furthermore, the very simple fMRI task was easily performed by the subjects even when ‘off’, and movement frequency was kept constant by auditory triggering and controlled by visual inspection of online pressure measurements.

Sequential fMRI measurements up to 120 min after L-dopa intake allowed us to correlate this motor cortex activation (related to the identically conducted task inside the scanner) with L-dopa-influenced motor performance, measured quantitatively outside the scanner after each session. Apart from the strong performance-correlated BOLD increase contralaterally to the clinically affected hand, we also found a smaller increase contralaterally to the clinically unaffected hand. This finding is not surprising since, according to PET studies in preclinical Parkinson’s disease (Brooks, 1991), a dopamine deficit contralateral to the clinically unaffected hand exists long before symptoms occur.

Although the BgT model suggests hypoactivity in M1 in Parkinson’s disease patients, results of previous brain imaging studies in this area are controversial. In an early SPECT study (Rascol et al., 1992), rCBF changes were measured in bilateral SMA and primary sensorimotor areas during a motor task similar to that used in our paradigm, with sequential finger-to-thumb opposition movements of the right hand in akinetic Parkinson’s disease patients in the ‘off’ and apomorphine-induced ‘on’ condition and in controls. Parkinson’s disease patients in the ‘on’ but not in the ‘off’ condition showed increased rCBF in both the SMA and the contralateral primary sensorimotor cortex but not in the ipsilateral primary sensorimotor cortex or other cortical areas. Recently, Parkinson’s disease patients who underwent pallidal stimulation were investigated with PET in a medication-free state in the ‘on’ and ‘off’ states (Fukuda et al., 2001), performing a predictable paced sequence of reaching movements. In line with our results in this study, a significant rCBF increase was found in the contralateral primary sensorimotor cortex and in bilateral SMA. In accordance with our data, improvement in motor performance (onset time and spatial error) was significantly correlated with the increase in rCBF mediated by stimulation. Like L-dopa, deep brain stimulation is believed to reduce the functional cortical deafferentation mediated by the motor circuit. The hypothesis of reduction of motor cortex inhibition by L-dopa in Parkinson’s disease is further supported by fMRI findings describing overactivity in the SMA and M1 of Parkinson’s disease patients with L-dopa-induced dyskinesia (Rascol et al., 1998).

In contrast, other investigators have found increased M1 activation in Parkinson’s disease patients compared with controls and/or an L-dopa-induced decrease in these areas (Jenkins et al., 1992; Haslinger et al., 2001). Jenkins and colleagues (Jenkins et al., 1992), using PET, found a significant activation increase in the contralateral primary
sensorimotor and PMC during a freely selected joystick movement compared with rest in Parkinson’s disease patients, in both the ‘off’ and the ‘on’ condition, but with no significant difference attributable to dopaminergic influences. The patients investigated used apomorphine regularly as a subcutaneous infusion in both conditions. Haslinger and colleagues (Haslinger et al., 2001), using fMRI and a joystick paradigm in early-stage Parkinson’s disease patients, found an L-dopa-induced decrease in signal levels in the M1, lateral premotor and superior parietal cortex. Compared with controls, Parkinson’s disease patients, both ‘off’ and ‘on’ L-dopa, showed increased activation levels in M1 and the lateral PMC bilaterally. The authors hypothesized that hyperactivity in M1 is caused by reorganization of an impaired motor system. Similar phenomena of cortical reorganization have been described in patients with functional recovery after stroke, in whom recruitment of the ipsilateral motor cortex might compensate for the contralateral deficit (Chollet et al., 1991; Weiller et al., 1992). According to this hypothesis, in Parkinson’s disease hyperactivity of M1 compensates for a deficiency in the basal ganglia system. Our data support this hypothesis indirectly by demonstrating that, in de novo early-stage Parkinson’s disease patients, reorganization of M1 is absent and hypoactivation of M1 and SMA, as expected, reflects decreased input arising from the subcortical motor loop, which is reversible by dopaminergic treatment. On the other hand, the M1 overactivity in Parkinson’s disease patients has generally been demonstrated during the performance of sequential or more complex movements rather than isolated limb movements. Further studies are required to investigate the impact of task complexity on the effects of L-dopa treatment in M1 and SMA.

Importantly, our data show that, in de novo parkinsonian patients, L-dopa leads to a performance-related BOLD signal increase not only in SMA but also in M1. This increase could, in theory, occur above the activation level in healthy controls, i.e. it could reflect hyperactivity that increases further after L-dopa treatment. However, the comparison with the healthy control group shows that finger movement-related activation in both SMA and M1 is significantly lower in untreated Parkinson’s disease patients during the ‘off’ phase. Most interestingly, the areas that show an increase related to performance after treatment within patients almost exactly overlap with those in which healthy volunteers show stronger activation than Parkinson’s disease patients, and this suggests that L-dopa treatment subsequently normalizes M1 and SMA ‘hypoactivation’.

According to the BgT model, in patients with moderate L-dopa-associated dyskinesia M1 and PMC hyperactivity has been described (Rascol et al., 1998; Brooks et al., 2000), suggestive of M1 activity increase caused by L-dopa. Ongoing dopaminergic treatment in previous studies might be responsible for the absence of increased M1 activity after L-dopa intake related to a persistent drug effect.

**Supplementary motor area activation before and after L-dopa intake**

Our findings suggest bilateral hypoactivity in SMA in early Parkinson’s disease, which is at least partially reversible by L-dopa. This is in line with the BgT model-generated hypothesis of functional cortical deafferentation and is supported by most previous brain imaging studies, which show reduced rCBF in SMA in Parkinson’s disease patients compared with controls, either during self-selected, externally triggered single joystick movements (Playford et al., 1992), finger movements (Rascol et al., 1992; Samuel et al., 1997) or, recently, in an fMRI study using more complex sequential movements (Sabatini et al., 2000). This last study found hypoactivity in rostral SMA, while in the caudal part of SMA overactivation was described (Sabatini et al., 2000).

Also, a previous PET study, investigating finger sequences in Parkinson’s disease patients, described hyperactivity of SMA (Catalan et al., 1999), which was interpreted as compensation for striatal dysfunction.

The reduced SMA activation in Parkinson’s disease patients was shown to be partly reversible through dopaminergic treatment with apomorphine (Jenkins et al., 1992) and L-dopa (Rascol et al., 1992) in previous PET studies and recently using fMRI (Haslinger et al., 2001). In advanced Parkinson’s disease patients, pallidal stimulation was shown to reduce akinesia in parallel with an increase in SMA activity (Fukuda et al., 2001). In our study, the L-dopa associated cortical increase in SMA was not as prominent as in M1 and was predominantly less prominent than described in the other studies (Jenkins et al., 1992; Rascol et al., 1992; Haslinger et al., 2001; Fukuda et al., 2001). One explanation might be that we used a very simple digit-to-thumb opposition motor task instead of a more complex joystick or sequential finger movement paradigm, as has been used in other studies. In contrast to previous studies, we only investigated patients who were naive to dopaminergic drugs and at an early stage of the disease. The main role of SMA is seen in the initiation of movement, which is diminished in Parkinson’s disease patients (Playford et al., 1992), and in the ability to prepare and perform alternative movements (Laplane et al., 1977). In early Parkinson’s disease stages these symptoms are less prominent, which would explain the smaller increase in SMA activity after L-dopa treatment in our study. Additionally, movement planning is less important in our simple motor task paradigm than in previous studies using more complex sequential or joystick motor tasks. This can also account for the fact that we did not observe activation in the dorsolateral prefrontal cortex and anterior cingulate and prefrontal cortex (Playford et al., 1992).

In conclusion, a performance-correlated increase in BOLD signal in cortical motor areas (M1 and SMA) after L-dopa intake supports the BgT model. At first sight, our results seem to be at odds with previous fMRI studies (Haslinger et al., 2001; Sabatini et al., 2000) showing M1 hyperactivity, as opposed to the M1 hypoactivity found in our data and
predicted by the BgT model. However, our data fully support the interpretation of M1 hyperactivity in these previous fMRI studies, namely that it is caused by reorganization, i.e. hyperactivity of M1 compensating for a deficient basal ganglia motor system. As expected, in strictly de novo Parkinson’s disease patients this reorganization is absent, as shown by our data.

Our data show that, in untreated Parkinson’s disease, hypoactivation of M1 and SMA reflects decreased input from the subcortical motor loop, which is reversible by dopaminergic treatment. This may have important implications for patients fulfilling the criteria of Parkinson’s disease but without L-dopa responsiveness, or for patients with parkinsonian syndromes other than Parkinson’s disease. A similar L-dopa challenge in combination with fMRI in these patients might help in the investigation of the pathophysiology of these diseases.

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