Corticostriatal functional interactions in Parkinson's disease: a rTMS/[11C]raclopride PET study

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Abstract

Several animal studies have shown that striatal dopamine can be released under direct control of glutamatergic corticostriatal efferents. In Parkinson's disease (PD), abnormalities in corticostriatal interactions are believed to play an important role in the pathophysiology of the disease. Previously, we have reported that, in healthy subjects, repetitive transcranial magnetic stimulation (rTMS) of motor cortex (MC) induces focal dopamine release in the ipsilateral putamen. In the present study, using [11C]raclopride PET, we sought to investigate early PD patients with evidence of unilateral motor symptoms. We measured in the putamen changes in extracellular dopamine concentration following rTMS (intensity, 90% of the resting motor threshold; frequency, 10 Hz) of the left and right MC. The main objective was to identify potential differences in corticostriatal dopamine release between the hemisphere associated with clear contralateral motor symptoms (symptomatic hemisphere) and the presymptomatic stage of the other hemisphere (asymptomatic hemisphere). Repetitive TMS of MC caused a binding reduction in the ipsilateral putamen of both hemispheres. In the symptomatic hemisphere, while the amount of TMS-induced dopamine release was, as expected, smaller, the size of the significant cluster of change in [11C]raclopride binding was, instead, 61.4% greater than in the asymptomatic hemisphere. This finding of a spatially enlarged area of dopamine release, following cortical stimulation, may represent a possible in vivo expression of a loss of functional segregation of cortical information to the striatum and an indirect evidence of abnormal corticostriatal transmission in early PD. This has potential implications for models of basal ganglia function in PD.

Keywords

Parkinson's disease; positron emission tomography; raclopride; motor cortex stimulation; transcranial magnetic stimulation

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Introduction

The striatum receives two major projections: glutamatergic from most of the cerebral cortex, and dopaminergic from the subtantia nigra and ventral tegmental area (Bouyer *et al.*, 1984; Sesack & Pickel, 1992). While several studies have attempted to investigate the functional abnormalities and compensatory mechanisms of the nigrostriatal dopaminergic system in Parkinson's disease (PD) (McGeer *et al.*, 1989; Zigmond *et al.*, 1990; Lee *et al.*, 2000), little attention has been paid to the role played by the corticostriatal system in the control of dopamine release in PD. The corticostriatal neurons belong to a series of recurrent parallel loops that project back to the cerebral cortex via the thalamus (Alexander *et al.*, 1986). The mesostriatal dopamine neurons, which are also arranged somatotopically, synapse on striatal medium spiny neurons in close proximity to the corticostriatal glutamatergic synapses, upon which they exert a modulatory influence (Bouyer *et al.*, 1984; Sesack & Pickel, 1992). Glutamate–dopamine interactions in the striatum play a major role in the normal function of the corticostriatal system, which is involved in a wide range of motor and cognitive functions that include planning of movement, procedural memory, attention, and reward processing. Moreover, abnormalities in glutamate–dopamine interactions are thought to play a role in the pathophysiology of disorders such as PD, schizophrenia and drug addiction (Carlsson & Carlsson, 1990).

Numerous animal experiments have demonstrated that the frontal cortex exerts an influence on striatal dopamine release (Murase *et al.*, 1993; Karreman & Moghaddam, 1996; Keck *et al.*, 2002; Kanno *et al.*, 2004), through the modulation of dopamine neuron firing (Murase *et al.*, 1993; Karreman & Moghddam, 1996), but possibly also through a direct effect of corticostriatal neurons on dopamine nerve terminals (Cheramy *et al.*, 1986; Leviel *et al.*, 1990).

In PD, abnormalities in corticostriatal interactions (Carlsson & Carlsson, 1990; Calabresi *et al.*, 1993, 2000) are believed to play an important role in the pathophysiology of the disease. In support of this hypothesis, electrophysiological studies in animal models of PD have shown an increased activation of corticostriatal glutamatergic transmission (Lindefors & Ungerstedt, 1990; Campbell & Bjorklund, 1994; Calabresi *et al.*, 2000) with an enhanced excitability of striatal target neurons (Calabresi *et al.*, 1993; Florio *et al.*, 1993; Campbell & Bjorklund, 1994; Onn & Grace, 1999; Calabresi *et al.*, 2000). These changes are associated with a functional reorganization of the cortical inputs to the striatum and a loss of functional segregation as also shown by the increase in cellular dye coupling between striatal neurons (Calabresi *et al.*, 1993, 2000;Florio *et al.*, 1993; Onn & Grace, 1999; Onn *et al.*, 2000). Together, the increased excitability of the corticostriatal pathway and the loss of functional segregation of cortical information to the striatum are believed to have important functional implications in the pathogenesis of PD motor symptoms (Calabresi *et al.*, 1993, 2000; Florio *et al.*, 1993; Onn & Grace, 1999).

Previous studies have shown that brain imaging, with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), and neurophysiological recordings, with electroencephalographic and single-cell recording, can be used to measure transcranial magnetic stimulation-induced changes in brain activity to study functional connectivity in

the human brain (Fox *et al.*, 1997; Paus *et al.*, 1998, 2001; Siebner *et al.*, 1998, 2003; Strafella & Paus, 2001; Strafella *et al.*, 2001, 2003, 2004; Bestmann *et al.*, 2004). Recently, we provided evidence supporting corticostriatal control of dopamine release in humans by using PET and the dopamine receptor ligand [^{11}C]raclopride to measure dopamine release in the striatum following repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (Strafella *et al.*, 2001) and motor cortex (Strafella *et al.*, 2003). Dopamine release was only detected focally in the ipsilateral caudate nucleus (Strafella *et al.*, 2001) and putamen (Strafella *et al.*, 2003).

In vivo binding of benzamide tracers such as [^{11}C]raclopride has been shown to be inversely proportional to levels of extracellular dopamine (Endres *et al.*, 1997; Laruelle, 2000). In humans, this method has also been used to measure dopamine release in response to drugs (Dewey *et al.*, 1993; Breier *et al.*, 1997; de la Fuente-Fernandez *et al.*, 2001, 2004; Piccini *et al.*, 2003; Stoessl & de la Fuente-Fernandez, 2003; Piccini, 2004) and to motor and behavioural tasks (Koepp *et al.*, 1998; Ouchi *et al.*, 2002; Goerendt *et al.*, 2003; Ginovart *et al.*, 2004).

In the present study, using [^{11}C]raclopride PET, we sought to investigate recently diagnosed, early, PD patients with evidence of unilateral symptoms. We measured in the putamen changes in extracellular dopamine concentration following rTMS (intensity 90% of the resting motor threshold, frequency 10 Hz) of the left and right primary motor cortex (MC). The main objective was to identify potential differences in corticostriatal dopamine release between the hemisphere clearly associated with contralateral motor symptoms and the presymptomatic stage of the other hemisphere in which, conceivably, functional compensatory mechanisms from surviving dopaminergic terminals (Zigmond *et al.*, 1990; McGeer *et al.*, 1989; Lee *et al.*, 2000) are still preventing the appearance of PD symptoms.

Materials and methods

Experimental design

Seven patients (Table 1), recently diagnosed with early unilateral PD (Hoehn–Yahr stages I), participated in the study after having given written informed consent. They were investigated, off medication after overnight withdrawal (12–18 h) of their antiparkinsonian medications, with [^{11}C]raclopride PET to measure changes in striatal dopamine release. Each underwent two [^{11}C]raclopride PET sessions (total injected dose 20 mCi), one after rTMS of the MC contralateral to the clinically affected hemibody (hereafter referred to as the symptomatic hemisphere) and one following rTMS of the MC contralateral to the asymptomatic side (hereafter referred to as the asymptomatic hemisphere). The scan order was randomized across subjects and the scans were performed at the same time on two consecutive days. Autonomic parameters and subjective ratings were collected throughout both test sessions. During the study the subjects were asked to relax and keep their eyes closed. The experiments were approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital.

Transcranial magnetic stimulation

Repetitive TMS was carried out with a Magstim high-speed magnetic stimulator (Magstim, UK). This device permits delivery of high-frequency magnetic stimuli through the same coil. TMS was delivered through a circular coil (9 cm external diameter) orientated so that the induced electric current flowed in a posterior–anterior direction over the hand area of the MC. The coil was held in the scanner in a fixed position by a mechanical arm over the area where the lowest motor threshold was obtained.

The motor threshold, which was determined for each individual prior to the PET session, was defined as the lowest stimulus intensity able to elicit, from the first dorsal interosseous (FDI), five motor evoked potentials (MEPs) of at least 50 µV amplitude in a series of 10 stimuli delivered over the MC at intervals > 5 s. MEPs were recorded with Ag-AgCl surface electrodes fixed on the skin with a belly tendon montage. Electromyogram (EMG) signal was filtered (50 Hz–50 KHz bandpass) and displayed on the EMGrapher screen (Keypoint, Medtronic, Canada).

The stimulation intensity was set at 90% of the resting motor threshold for the FDI to avoid EMG responses. Four rTMS blocks were delivered 10 min apart in the scanner prior to image acquisition. Each block consisted of 15 10-pulse trains of 1 s duration (i.e. 10 Hz) with an intertrain interval of 10 s. Subthreshold rTMS over either of the stimulation sites induced no EMG responses in the relaxed FDI or in the abductor pollicis brevis or extensor digitorum communis.

Subjective ratings and autonomic measures

Electrodermal level, respiration rate and temperature were measured for 2.5 min during a baseline period at the start of the study and during the rest periods following each block of rTMS. After the baseline period and after each rest period, subjects rated their level of comfort, fatigue, anxiety, mood, irritation and pain on a seven-point Likert scale ranging from −3 to +3. For the baseline ratings, subjects were asked to rate how they were currently feeling, while ratings following blocks of rTMS referred to how they felt during the preceding rTMS stimulation. The autonomic and behavioural measures were analysed using repeated-measures ANOVA.

PET and imaging analysis

PET scans were obtained with a CTI-Siemens HR plus tomograph operating in 3-D mode, yielding images of resolution 4.2 mm full-width at half-maximum. Within 5 min of the end of the rTMS session, 10 mCi of [^{11}C]raclopride was injected into the left antecubital vein over 60 s and emission data were then acquired over a period of 60 min in 26 frames of progressively increasing duration. After the emission scan, a 10-min transmission scan was performed with a rotating radioactive source (^{68}Ga) for attenuation correction.

Each hemi-parkinsonian patient underwent two [^{11}C]raclopride PET sessions, one after rTMS of the MC of the symptomatic hemisphere and one after rTMS of the MC of the asymptomatic hemisphere. The effect of rTMS on striatal dopamine release is strictly limited to the ipsilateral hemisphere (Strafella *et al.*, 2001, 2003); thus, the change in striatal

[^{11}C]raclopride binding potential (BP) of the stimulated hemisphere was compared with the ipsilateral striatal [^{11}C]raclopride BP of the nonstimulated hemisphere of the other session (baseline).

A high-resolution MRI (Siemens Sonata 1.5 T; T1-weighted images, 1 mm slice thickness) of each subject's brain was acquired and transformed into standardized stereotaxic space (Talairach & Tournoux, 1998) using automated feature-matching to the Montreal Neurological Institute template (Collins *et al.*, 1994).

PET frames were summed, registered to the corresponding MRI (Woods *et al.*, 1993) and transformed into standardized stereotaxic space using the transformation parameters previously determined for the MRI. Thus, coordinates listed in the results are in Talairach space and correspond to the so-called MNI305 template. Voxelwise [^{11}C]raclopride BP was calculated using a simplified reference tissue (cerebellum) method (Lammertsma & Hume, 1996; Gunn *et al.*, 1997) to generate statistical parametric images of change in BP (Aston *et al.*, 2000). This method uses the residuals of the least-squares fit of the compartmental model to the data at each voxel to estimate the standard deviation of the BP estimate, thus greatly increasing degrees of freedom. Only peaks falling within the striatum were considered, because this is the only brain structure where receptor-specific [^{11}C]raclopride binding is detected. A reduction in [^{11}C]raclopride BP is indicative of an increase in extracellular dopamine concentration (Dewey *et al.*, 1993; Breier *et al.*, 1997). For the purpose of the group analysis, images were flipped along the horizontal axis so that the side of all symptomatic hemispheres was set on the left while the asymptomatic hemisphere was on the right.

A threshold level of $t \geq 4.2$ was considered significant ($P < 0.05$, two-tailed) corrected for multiple comparisons (Worsley *et al.*, 1996), assuming a search volume equal to the entire striatum, an effective image filter of 6 mm full-width at half-maximum and 276 degrees of freedom (Aston *et al.*, 2000). In each subject, BP values of the putamen were extracted with spherical regions of interest (radius 5 mm) drawn on the MRI at the level of the statistical peak defined by the parametric map (asymptomatic hemisphere, $x = 35$, $y = 4$, $z = 0$; symptomatic hemisphere, $x = -30$, $y = 7$, $z = 5$).

Results

Repetitive TMS of the MC was associated with a reduction in [^{11}C]raclopride BP in the ipsilateral putamen of both the asymptomatic and the symptomatic hemisphere (Fig. 1A). This reduction in [^{11}C]raclopride BP is indicative of an increase in dopamine neurotransmission following cortical stimulation.

In the asymptomatic hemisphere, rTMS of the MC induced a 12.99% decrease in [^{11}C]raclopride BP (mean ± SD: baseline, 1.847 ± 0.22; rTMS, 1.607 ± 0.20) whereas, in the symptomatic hemisphere, rTMS produced a 9.47% reduction in BP (baseline, 1.762 ± 0.36; rTMS, 1.595 ± 0.30). The magnitude of change in binding was significantly less in the putamen of the symptomatic hemisphere (ANCOVA after adjusting for baseline differences, $F_{1,5} = 19.75$, $P < 0.01$). Figure 2 displays percentage changes and BP values

from the putamen of the asymptomatic and symptomatic hemisphere obtained from regions of interest drawn at the axial level of the statistical peaks.

The area of decrease in [11C]raclopride BP, located in the lateral part of the putamen, had its peak at coordinates $x = 35$, $y = 4$, $z = 0$ for the asymptomatic hemisphere and at $x = -30$, $y = 7$, $z = 5$ for the symptomatic hemisphere. While in the former the significant cluster, extending from $y = -2$ to $y = 7$ in the anteroposterior direction (where $y = 0$ mm is the level of the anterior commissure), involved 70 voxels, corresponding to a volume of 560 mm^3, in the latter the significant cluster, extending from $y = -6$ to $y = 12$, counted 113 voxels corresponding to a volume of 904 mm^3 (Fig. 1B). This represented an increase in cluster size for the symptomatic hemisphere of 61.4%.

These changes in [11C]raclopride BP were not related to the stimulation intensity. There were no statistically significant differences in any other striatal areas (i.e. caudate nucleus or nucleus accumbens), nor was any difference observed in motor threshold between the symptomatic (mean $\pm$ SD, 49.1 $\pm$ 0.98%) and asymptomatic (50.6% $\pm$ 2.73%) hemispheres. The statistical analysis of autonomic and behavioural measures revealed no significant main effect of stimulation site or condition (before and after rTMS), nor any significant site $\times$ condition interaction (Tables 2 and 3).

Discussion

We have shown that rTMS of the human MC in hemi-parkinsonian patients evoked release of dopamine in the ipsilateral putamen, as detected by [11C]raclopride PET. The most interesting finding was that, in the symptomatic hemisphere, while the amount of TMS-induced striatal dopamine release was, as expected, smaller, the size of the significant cluster of change in [11C]raclopride BP was, instead, 61.4% greater than in the asymptomatic side (Figs 1 and 2).

The observed changes in [11C]raclopride BP in the ipsilateral putamen of patients with PD confirms our previous experiments performed in normal subjects in which we showed that rTMS of the dorsolateral prefrontal cortex and motor cortex was associated with reduced [11C]raclopride binding in its main projection area of the striatum, namely the ipsilateral head of the caudate nucleus (Strafella *et al.*, 2001) and putamen (Strafella *et al.*, 2003). The putamen is the principal input nucleus for somatic motor control in the basal ganglia and receives somatotopically organized corticostriatal projections from the frontal motor areas (Kemp & Powel, 1970; Kunzle, 1975; Jones *et al.*, 1977; Liles & Updyke, 1985; Whitworth *et al.*, 1991; Parent & Hazrati, 1995; Inase *et al.*, 1996; Takada *et al.*, 1998; Tokuno *et al.*, 1999). Anterograde tracing studies in monkeys have shown that corticostriatal fibers originating in the MC project to the lateral part of the putamen with a dorsoventral arrangement, the leg represented in the dorsal putamen, the face more ventrally and the arm lying in between these two areas (Jones *et al.*, 1977; Kunzle, 1975; Liles & Updyke, 1985; Whitworth *et al.*, 1991; Takada *et al.*, 1998). Moreover, in monkeys there is distal-to-proximal somatotopy, with the distal forelimb portion of the MC projecting to the most lateral part of the putamen (Tokuno *et al.*, 1999). This anatomical location corresponds exactly to the cluster of dopamine release found in our present study following stimulation

of the hand area of the MC (Fig. 1A). This is also in accordance with our previous report of dopamine release confined to the lateral part of the ipsilateral putamen following rTMS of the finger representation in the MC (Strafella *et al.*, 2003).

One limitation of the present study relates to the brain area stimulated by our rTMS. While the hand MC projections were certainly stimulated, we cannot exclude the possibility that adjacent cortical areas, namely premotor and somatosensory cortex, were also stimulated, which may have contributed to dopamine release. However, the premotor corticostriatal projections map to the dorsomedial putamen (Takada *et al.*, 1998), where there was no change in tracer binding. The somatosensory corticostriatal projections target the same areas as MC in the lateral putamen (Flaherty & Graybiel, 1993).

Although a direct corticostriatal influence on striatal dopamine terminals most probably accounts for the spatial selectivity of the rTMS effect in our study, we cannot exclude involvement of other anatomical pathways. Frontal cortical neurons also project to the substantia nigra (Sesack & Pickel, 1992; Naito & Kita, 1994) where they can modulate the firing of dopamine neurons projecting to the striatum (Murase *et al.*, 1993; Karreman & Moghddam, 1996). However, little is known about the somatotopic organization of this system.

In the present study, the amount of TMS-induced striatal dopamine release was less in the symptomatic hemisphere than in the contralateral hemisphere. This was not surprising, and two main reasons could account for this finding: the more advanced degeneration of dopaminergic terminals and the failure of the well described functional compensatory mechanisms from surviving dopaminergic terminals (McGeer *et al.*, 1989; Zigmond *et al.*, 1990; Lee *et al.*, 2000), which are mainly characterized by an increase in synthesis and release of dopamine as well as by a reduced dopamine inactivation rate in the presynaptic space of nerve terminals (Zigmond *et al.*, 1990; Lee *et al.*, 2000).

The most intriguing and, we believe, exciting finding of this study was the larger cluster of change in [^{11}C]raclopride BP (61.4%) involving the symptomatic side (Fig. 1A and B). There are a number of possible interpretations that could explain our observation. Indeed, Zigmond *et al.* (1990) have suggested that the field of influence of residual dopamine terminals increases with denervation. That is, because of the partial loss of re-uptake sites, released dopamine diffuses out to more distant regions of the receptor population in the dopamine-denervated striatum. According to this model, dopamine molecules released after rTMS could possibly interact with larger areas of the receptor population in the symptomatic putamen. However, several electrophysiological studies have also shown that in conditions of dopamine denervation there exists a hyperactivity of corticostriatal glutamatergic transmission (Lindefors & Ungerstedt, 1990; Calabresi *et al.*, 1993, 2000; Campbell & Bjorklund, 1994) with increased numbers of striatal neurons responding to cortical stimulation (Florio *et al.*, 1993). Therefore, as an alternative, one may propose that because of such corticostriatal hyperactivity rTMS could be responsible for an abnormal release of glutamate which by diffusing into the extrasynaptic space (Onn *et al.*, 2000) may activate, either directly or indirectly via nitric oxide (Onn *et al.*, 2000), larger areas of dopaminergic terminals in the symptomatic hemisphere.

While there is certainly little knowledge about the mechanisms by which rTMS exerts remote effects, either one of the proposed explanations seem to support the hypothesis that the larger cluster of change in [^{11}C]raclopride BP in the symptomatic hemisphere (where compensatory mechanisms have presumably failed) may represent an *in vivo* measure of a loss of functional segregation of cortical information to the striatum, thus representing indirect evidence of abnormal corticostriatal transmission in symptomatic PD.

In contrast, the more focal release of dopamine observed in the putamen of the contralateral hemisphere in the presymptomatic stage (Fig. 1A and B), similar to what has also been described in normal subjects (Strafella *et al.*, 2003) may well represent the result of the functional compensatory changes (McGeer *et al.*, 1989; Zigmond *et al.*, 1990; Lee *et al.*, 2000) taking place in these patients and still preventing the appearance of the motor symptoms.

The finding of a spatially enlarged area of dopamine release following cortical stimulation as a possible indirect expression of loss of functional segregation of striatal neurons has implications for models of basal ganglia function in PD. One of these models proposes that, during action, there is specific enhancement of activity in corticostriatal loops involved in the current task with concomitant suppression of competing motor networks (Mink, 1996). The neuroanatomical arrangement of the corticostriatal system in a centre-surround inhibitory pattern is thought to facilitate this focusing function (Parent & Hazrati, 1993; Mink, 1996; Mink, 2003). The abnormal corticostriatal excitability and loss of neuronal functional segregation described in PD may well contribute to the de-arrangement of this selective centre-surround inhibitory pattern leading to an impaired inhibition of competing motor patterns and underlying some of the motor symptoms observed in this condition.

Our findings open new avenues for two different types of *in vivo* studies in PD. In the first place, the opportunity for longitudinal studies, to test whether the enlarged area of dopamine release as a consequence of the corticostriatal activation is simply a nonspecific sign of PD or could possibly be considered an index for the later development of motor fluctuations (i.e. dyskinesias). In the second place, the possibility of testing the capability of antiparkinsonian medications (i.e. L-dopa, dopamine agonists) in restoring (or worsening) spatially confined area of dopamine release, as observed in healthy subjects.

Acknowledgments

Abbreviations

BP	binding potential
EMG	electromyogram
FDI	first dorsal interosseous

fMRI	functional magnetic resonance imaging
MC	motor cortex
MEP	motor evoked potential
PD	Parkinson's disease
PET	positron emission tomography
rTMS	repetitive transcranial magnetic stimulation

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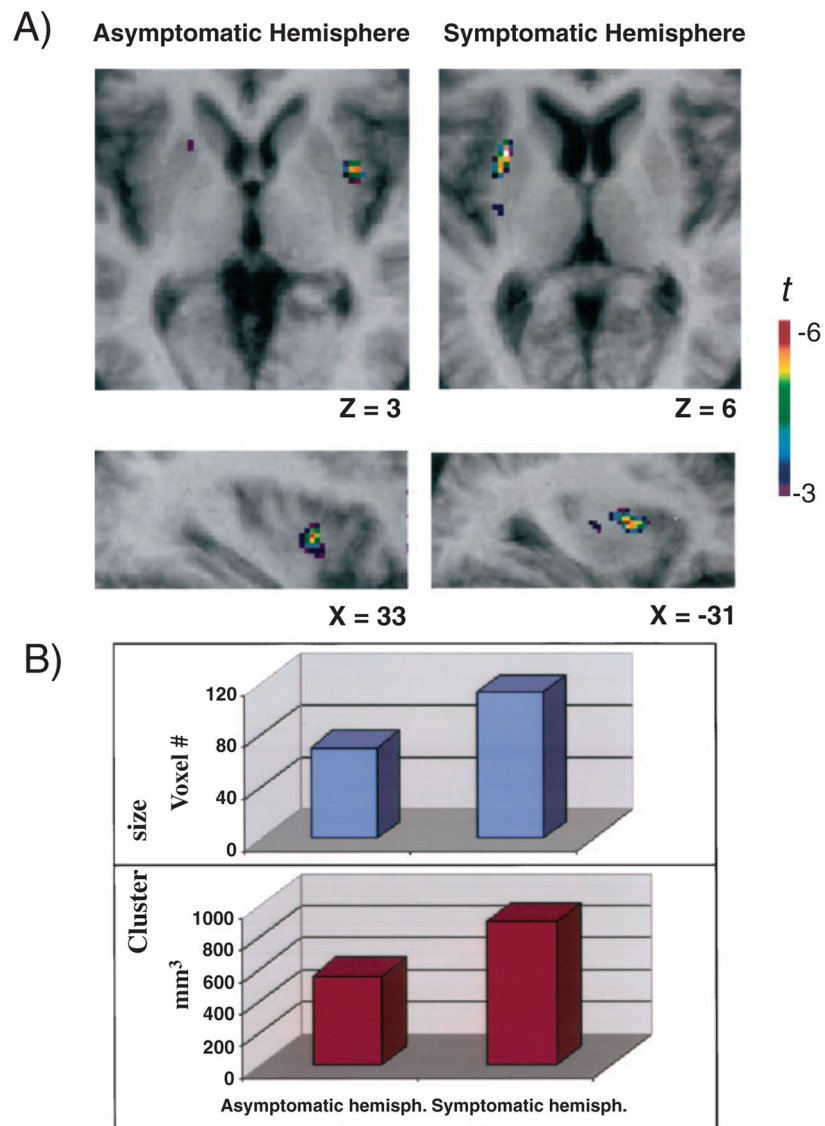
Fig. 1.
rTMS-induced dopamine release. (A) Axial and sagittal sections of the statistical parametric map of the change in [^{11}C]raclopride BP overlaid upon the average MRI of all subjects in stereotaxic space. (B) The figure displays the size (voxel number and mm^3) of the significant cluster of dopamine release in the putamen for the asymptomatic and symptomatic hemispheres.
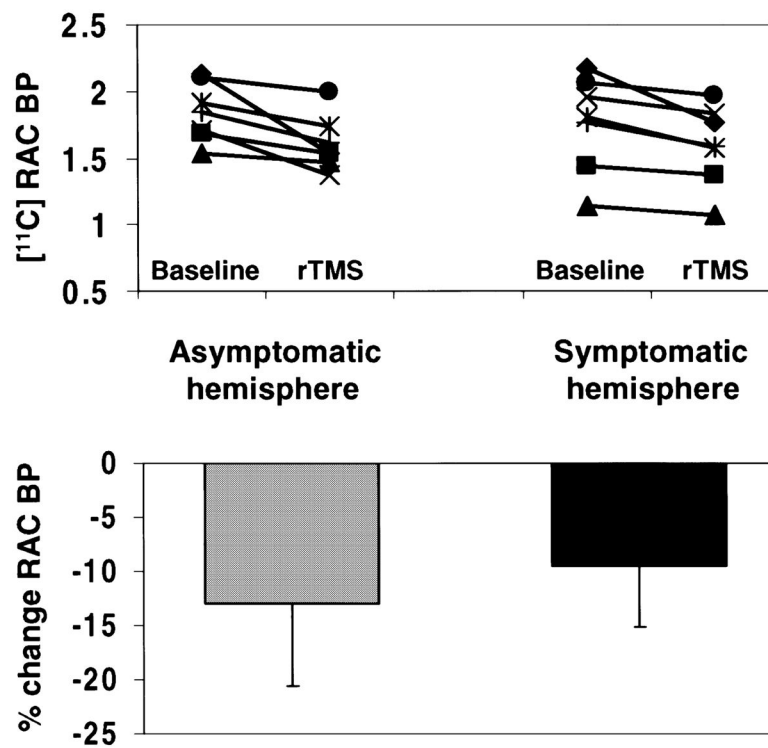
Fig. 2.
Binding potentials. On the top, [^{11}C]raclopride binding potentials (baseline and following rTMS), from the putamen of the asymptomatic (left) and symptomatic (right) hemispheres, extracted from a spherical region of interest (radius 5 mm) centred at the *x*, *y*, and *z* coordinates of the statistical peak revealed by the parametric map. On the bottom, the figure displays the percentage changes in [^{11}C]raclopride BP for the asymptomatic (left) and symptomatic (right) hemispheres. The magnitude of change in binding was significantly less in the putamen of the symptomatic than the asymptomatic hemisphere ($P < 0.01$ by ANCOVA after adjusting for baseline differences).

Table 1

Clinical features of PD patients

Subject	Age (years)	Disease duration (months)	UPDRS* (III) off medication	Medication	Dose (mg/day)
1	61	11	19	Pramipexole	1.5
2	66	8	13	Levodopa	100
3	58	12	17	Pramipexole	0.75
4	60	13	19	Levodopa	100
5	57	11	17	Pramipexole	1.5
6	40	9	14	None	–
7	53	10	17	Pramipexole	0.75
Mean ± SD	56.4 ± 8.26	10.5 ± 1.71	16.5 ± 2.2		

UPDRS III, Unified Parkinson's Disease Rating Scale, motor section.

*
Values are divided by 108.

Table 2

Mean autonomic parameters before and after rTMS of symptomatic and asymptomatic hemisphere

	Symptomatic hemisphere		Asymptomatic hemisphere	
	Before rTMS	After rTMS	Before rTMS	After rTMS
Electrodermal level (μΩ)	5.88 ± 0.47	5.62 ± 0.47	5.50 ± 0.24	5.45 ± 0.26
Respiration rate	9.14 ± 2.46	9.74 ± 2.95	8.70 ± 1.98	8.66 ± 1.26
Temperature (°C)	27.91 ± 2.78	28.35 ± 2.86	31.21 ± 2.77	29.86 ± 3.87

Mean values are shown ±SD.

Table 3

Behavioural ratings before and after rTMS of symptomatic and asymptomatic hemisphere[*]

	Symptomatic hemisphere		Asymptomatic hemisphere	
	Before rTMS	After rTMS	Before rTMS	After rTMS
Discomfort–comfort	1.78 ± 1.20	1.98 ± 0.98	1.22 ± 1.92	1.19 ± 1.78
Anxious–calm	1.22 ± 2.11	1.37 ± 2.00	1.44 ± 1.94	1.37 ± 1.94
Fatigued–rested	1.33 ± 1.87	1.30 ± 1.76	1.44 ± 1.01	1.58 ± 1.00
Sad–happy	1.56 ± 1.24	1.44 ± 1.13	1.28 ± 1.25	1.35 ± 1.22
Irritated–soothed	1.11 ± 1.90	1.11 ± 1.90	1.06 ± 1.98	0.96 ± 2.01
Feel pain–do not feel pain	1.33 ± 1.41	1.47 ± 1.10	1.44 ± 1.24	1.50 ± 1.21

[*]
Seven-point Likert scale, ranging from −3 to +3. Values are presented as mean ± SD.