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What can man do without basal ganglia motor output? The effect of combined unilateral subthalamotomy and pallidotomy in a patient with Parkinson's disease

J.A. Obeso [a,e,*], M. Jahanshahi [b], L. Alvarez [c], R. Macias [c], I. Pedroso [c], L. Wilkinson [b], N. Pavon [c], B. Day [b], S. Pinto [b], M.C. Rodríguez-Oroz [a,e], J. Tejeiro [c], J. Artieda [a], P. Talelli [b], O. Swayne [b], R. Rodríguez [c], K. Bhatia [b], M. Rodriguez-Diaz [d,e], G. Lopez [c], J. Guridi [a,e], J.C. Rothwell [b]

[a] Department of Neurology, Clínica Universitaria and Medical School of Navarra, Neuroscience Centre, CIMA, University of Navarra and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Instituto Carlos III, Ministerio de Investigación y Ciencias, Madrid, Spain
[b] Sobell Department of Motor Neurosicence and Movement Disorders, Institute of Neurology, University College, London, England
[c] Movement Disorders and Neurophysiology Units, Centro Internacional de Restauración Neurológica (CIREN), La Habana, Cuba
[d] Department of Physiology, Medical School, Universidad de La Laguna, Tenerife, Spain
[e] Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain

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ABSTRACT

We have studied motor performance in a man with Parkinson's disease (PD) in whom thermolytic lesions of the left subthalamic and left globus pallidus nuclei interrupted the basal ganglia (BG)-thalamo-cortical motor circuit in the left hemisphere. This allowed us to study remaining motor capabilities in the absence of aberrant BG activity typical of PD. Movements of the left arm were slow and parkinsonian whereas movement speed and simple reaction times (RT) of the right (operated) arm were within the normal range with no obvious deficits in a range of daily life activities. Two main abnormalities were found with the right hand. (a) Implicit sequence learning in a probabilistic serial reaction time task was absent. (b) In a go/no-go task when the percent of no-go trials increased, the RT superiority with the right hand was lost. These deficits are best explained by a failure of the cortex, deprived of BG input, to facilitate responses in a probabilistic context. Our findings confirm the idea that it is better to stop BG activity than allowing faulty activity to disrupt the motor system but dispute earlier claims that interrupting BG output in PD goes without an apparent deficit. From a practical viewpoint, our observations indicate that the risk of persistent dyskinesias need not be viewed as a contraindication to subthalamotomy in PD patients since they can be eliminated if necessary by a subsequent pallidotomy without producing deficits that impair activities of daily life.

Introduction

Precise understanding of the function of the basal ganglia (BG) in motor control remains elusive. The pathophysiological model developed in the late 1989 divided striato-pallidal projections into the "direct" and "indirect" circuits. The former being implicated in movement facilitation and the latter in movement inhibition. In that model, lack of striatal dopamine input in Parkinson's disease (PD) reduced activity in the direct pathway and increased activity in the indirect pathway leading to increased inhibitory output from the pallidum and reduced thalamic facilitation of motor cortex, which was posited as the basis for bradykinesia (Albin et al., 1986; Crossman, 1987; DeLong, 1990).

The accumulated evidence from contemporary surgery of the BG has highlighted two recognized paradoxes of the original BG model, namely, that pallidotomy eliminates dyskinesias (including levodopa-induced dyskinesias), when the opposite would be expected, and the absence of obvious additional motor deficits following ablative surgery of the BG or thalamus in patients with PD (Marsden and Obeso, 1994; Brown and Eusebio, 2008). In recent years the model has been refined to include the importance of neuronal patterns of discharge within the BG and its degree of synchrony with target structures (Wichmann and DeLong, 1996; Lozano et al., 2000; Obeso et al., 2000; Vitek and Giroux, 2000; Brown and Eusebio, 2008). The underlying implication is that surgery may improve both parkinsonian features and dyskinesias by removing or blocking the abnormal firing patterns that interfere with other components of the motor system (Mink, 1996; Lozano et al., 2000; Vitek and Giroux, 2000; Alonso-Frech et al., 2006). On the other hand, how the BG and thalamus tolerate the effect of lesions is still not well explained. To some extent, the patient described here provides the opportunity to assess the contribution of the BG to motor control. Subthalamotomy is routinely performed in the Centro Internacional de Restauración Neurológica (CIREN, La Habana, Cuba) as a surgical alternative to deep brain stimulation (DBS) (Alvarez et al., 2001, 2005, 2009). Following a thermolytic lesion of the subthalamic nucleus (STN), patients often develop transient hemichorea or hemiballism that

* Corresponding author. Fax: +34 948 194600.
E-mail address: jobeso@unav.es (J.A. Obeso).

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in most instances resolves spontaneously within hours or days while motor improvement remains. However, in a minor proportion (around 8%) of patients the hemichorea-ballism may be severe and persistent enough to warrant placing a second lesion in the motor region of the globus pallidum pars interna (GPi), which is well known to eradicate hemichorea-ballism following STN lesions both in monkeys and humans (Carpenter et al., 1950; Suarez et al., 1997; Alvarez et al., 2009). We have studied one of these patients who received sequential STN and GPi lesions in the most affected (parkinsonian) hemisphere. This effectively leads to a functional removal of the cortico-BG-thalamo-cortical motor loop (Fig. 1A), thus allowing us to explore what a person can or cannot do with his limbs when deprived, by and large, of BG output to the motor cortex in one hemisphere.

Case report (see full description and video in supplementary material)

The patient described here is one of seven patients with PD similarly operated in the CIREN as part of an ongoing subthalamotomy project (Alvarez et al., 2001, 2005, 2009). In all of them the initial subthalamotomy was associated with hemichorea-ballism which required treatment with a pallidotomy within the next few weeks or months. The clinical features and observations regarding movement control of the patient described here are representative of the whole group. He was chosen for this pilot project because of his excellent general health, adequate educational level (school teacher) and a very favorable personal attitude to participate in the study. RP is a 53-year-old right handed man with a 12-year history of PD starting by clumsiness and tremor of the right arm then spreading to the right leg to become generalized after a few years. Initial response to levodopa (600 mg daily) was excellent but after 4 years "wearing off" motor fluctuations and "peak of dose" or "on" dyskinesias in the neck and right extremities developed. These complications became more severe and difficult to manage over the following years despite repeated treatment adjustments. Before surgery (January 2003), UPDRS (Unified Parkinson's Disease Rating Scale) motor (part-III) in the "off" medication (24 h after last dose) state was 46; motor signs were more severe in the right limbs with predominant bradykinesia, tremor and rigidity of the upper limb as well as axial and facial involvement. UPDRS in the "on" was 11 with a dyskinesias score of 2/4 (CAPIT scale) predominating in neck and right shoulder. In December 2003, a left unilateral subthalamotomy was associated with right hemichorea, beginning immediately after surgery, which reached ballistic magnitude in the right leg over the next 24 h. This did not abate during the next 3 weeks despite withdrawing all anti-parkinsonian medications. Thus, a left pallidotomy targeted to lesion mainly the posterior region of the GPi was performed 23 days after the initial subthalamotomy (Fig. 1B; further information in complementary material). This stopped the hemi-dyskinesias within the operating room without noticeable side-effects. The patient remained very stable and was discharged without complications on treatment with levodopa/benserazide 300 mg/day.

When evaluated in June 2005, UPDRS motor in "off" (16 h without medication) was 21 mainly due to parkinsonian signs in the left side, moderate hypophonia and mild facial hypomimia (see videotape in supplementary material). The only parkinsonian signs in the right limbs consisted of mild bradykinesia with the hand and fingers and cog-wheel rigidity in the upper limbs when moving other body parts (Froment's signs). In the "on" motor state (i.e., 1–2 h after taking 100/25 mg of levodopa/benserazide) UPDRS motor was 9. In the "on" state improvement was bilateral, with both sides showing similar UPDRS motor scores (see video in complementary material). Mild dyskinesias in left shoulder and neck were present. Cognitive evaluation in different cognitive domains (memory, executive function, language and visuospatial function) was normal as evaluated with an extensive neuropsychological battery including, in addition to the global MMSE, the following tests: Stroop, Trail making, Raven's Progressive Matrices, phonemic and semantic verbal fluency, Boston word naming test, copy and retrieval of geometric figures and Buschke selective reminding test. Speech was completely normal. On daily life activities RP performed normally. He could undertake all sorts of tasks without any difficulty and used his right upper limb with extreme efficiency. Automatic movements such as saluting, writing and eating while talking were performed with ease. At the last (March 2008) neurological examination he remained stable (UPDRS motor in "on" of 18) but facial and neck dyskinesias had worsened.

MRI of the brain repeated in 2005 showed the STN and pallidal lesions, although reduced in size as expected for the long-term appearance of a thermolytic lesion. An 18-fluorodopa PET (positron emission tomography) revealed a bilateral reduction in the decarboxylation constant (K_i) but more accentuated in the left striatum and particularly in the left posterior putamen (supplementary figure).

Methods

Most studies were performed both "on" and "off" therapy, with the latter defined as a minimum of 24 h without receiving any anti-parkinsonian medication. The study includes a series of motor tests

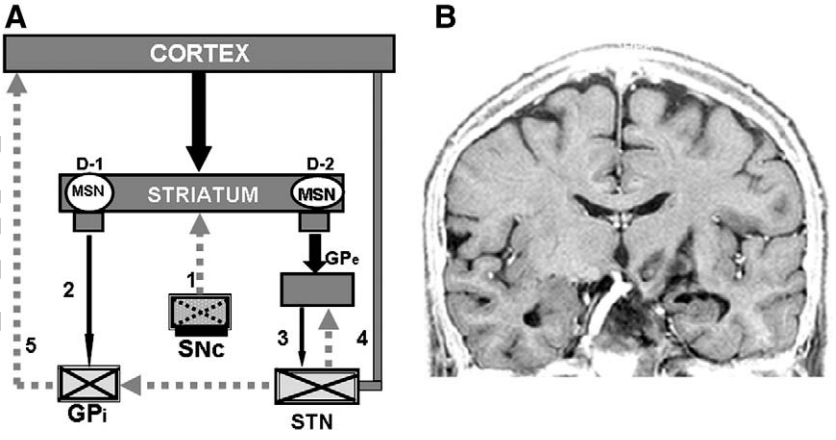

Fig. 1. (A) Schematic summary of the main basal ganglia connections interrupted in patient RP. There is degeneration of the substantia nigra pars compacta (SNc) and dopamine striatal depletion (1) as a result of Parkinson's disease, which is associated with hypoactivity of D-1 expressing medium spiny neurons (MSN) in the "direct" striato-pallidal projection (2). Lesion of the subthalamic nucleus (STN) interrupted the connections with the globus pallidus pars externa (GPe) in the "indirect" circuit (3) and the cortico-subthalamic "hyper-direct" pathway (4) with the globus pallidus pars interna (GPi). Lesion of the GPi blocked basal ganglia output (5) to the thalamo-cortical projection. (B) Magnetic resonance (coronal section) showing the lesion in the posteroventral region of the GPi and the dorsolateral region of the STN about 4 weeks after surgery.

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Table 1

Task	Test	Function measured	PD	Patient RP	
				Left	Right
I. Movement and reflexes					
Lift index	Simple reaction time	Preparation and initiation	↑	↑	↓
Elbow flexion	Mov. time	Selection and recruitment	↑	↑	↓
Simultaneous elbow flexion and squeeze	Mov. time	Selection and execution of 2 different movements	↑	↑	↓
Arm rising on standing	Postural reflexes	Muscle recruitment order	↓	N	N
II. Cortical excitability and activation pattern					
TMS	(a) Motor threshold	Cortical excitability	↑	N	N
	(b) Intracortical inhibition	Idem	↓	↓	↓
	(c) Silent period	Idem	↓	↓	N
fMRI	Left vs. right hand free selection of direction of joystick movements	Movement-related cerebral activation	↓	–	N
III. Time estimation					
Intervals between pair stimuli	TDT	Internal time representation	↓	↓	↑
IV. Decision to respond or withhold a response					
Go/no-go RT	Move in response to go signal and withhold response on no-go trials	Action initiation	↓	↓	↓[a]
V. Implicit sequence learning					
Probabilistic SRTT	Press response bottom according with position of visual signal	Implicit sequence learning	↓	↓	Absent

Abbreviations: TMS, transcranial magnetic stimulation; fMRI, functional magnetic resonance imaging; TDT, temporal discrimination threshold.
[a] Deteriorated when the ratio of "go/no-go" trials were 25/75%.

(Table 1) that explore the RP's ability to prepare, select and execute movements at single and multiple joints. The excitability of the motor cortex was assessed by transcranial magnetic stimulation (Kujirai et al., 1993; Ridding and Rothwell, 1999) and functional MRI evaluated patterns of movement related activity in the whole brain. Complex motor tasks such as implicit sequence learning and response initiation and suppression in a go/no-go trial were assessed as well as his ability to estimate time intervals in a non-motor task (Table 1). All of these functions are known to be affected in patients with PD and are thought to reflect activity in the BG and its cortical projections. Detail technical explanations for each of the test applied in the study are given as supplementary material.

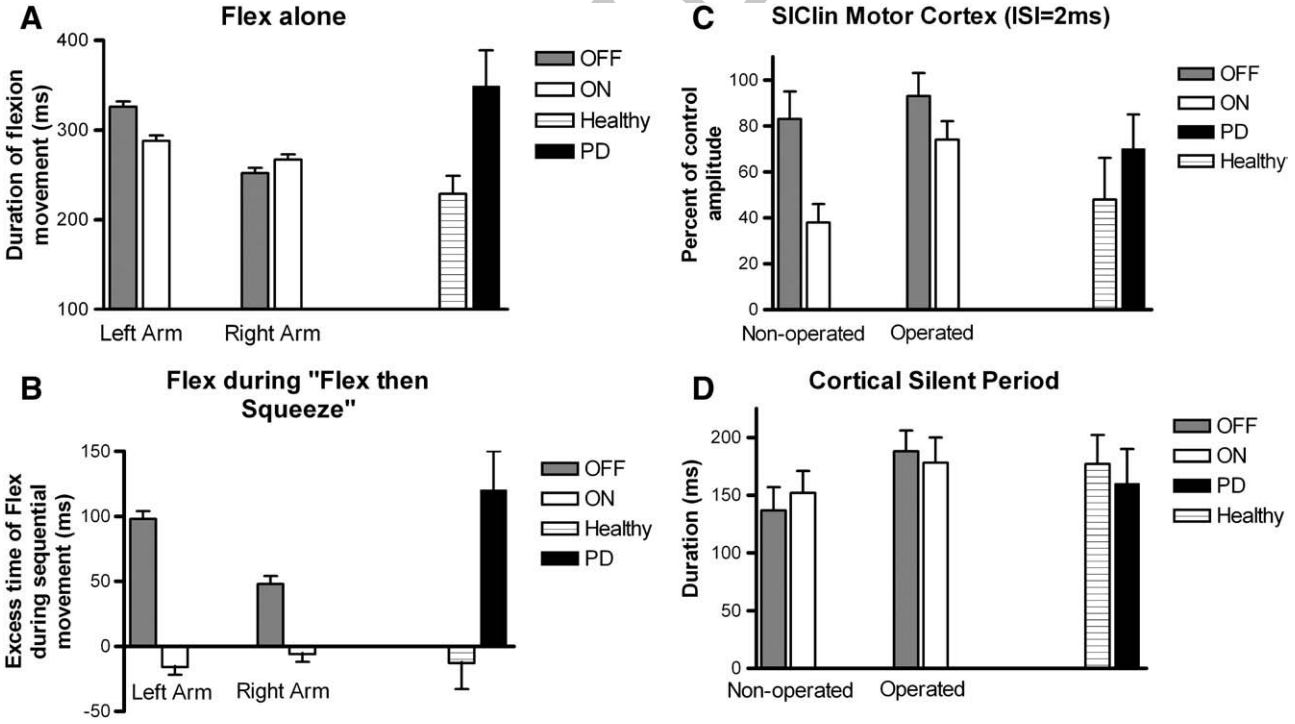

Fig. 2. Movement kinematics (A and B) and transcranial magnetic cortical stimulation data (C and D) in the patient compared with a group of age-matched healthy controls and a group of moderately affected patients with PD. Data are mean ± SE of the trial-by-trial data of the patient, and the inter-subjects means of the control groups. (A) Time taken to execute a 30% self paced isotonic elbow flexion task from movement onset to peak of movement. (B) Excess time taken to perform the flexion component of a simultaneous "flex and squeeze" task over and above the time for the flexion component to be executed separately on its own. (C) Mean percent short interval intracortical inhibition in the relaxed FDI muscle at interstimulus intervals of 2–3 ms. Inhibition is measured as the size of the conditioned MEP as a percent of the unconditioned control MEP. (D) Duration of the EMG silent period following the MEP measured from stimulus onset to resumption of ongoing background EMG activity. Stimulus intensity 1405 resting motor threshold applied during an approximate 30–50% contraction of the FDI muscle.

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Results

Tests improved or not worsened by lesions

Movement kinematics

The graphs in Fig 2A and B show mean data from a group of age-matched healthy controls and a group of comparable (age, disease severity and duration, treatment, etc.) patients with PD "off" therapy for comparison with the results of patient RP (patients reported in Benecke et al., 1987). In general, patients with PD take longer than normal to flex their elbow through 30° (Fig. 2A) and when they perform the same task at the same time as squeezing a force transducer in their hand (Fig. 2B; "flex and squeeze" task), the time taken to flex the elbow increases still further. RP also took longer for the dual than the single task but the deficit was significantly larger for left arm movements ($p<0.01$) which fall within the range of typical PD patients. Movements of both arms normalized in the "on" state. Further details are provided in supplementary material.

Repetitive clenching of both hands simultaneously (Supplementary Fig. S2) in the "off" state showed the same frequency for both hands but the amplitude of movement with the left hand decreased gradually over time.

Anticipatory postural adjustments

Postural adjustments were assessed during rapid elevation of each arm independently in the "off" state (Fig. 3). RP exhibited a normal pattern of muscular activation prior to movement onset. The left arm was raised more slowly than the right, but there was an early postural muscle synergy for movements of either arm that began with a reduction of activity in ipsilateral triceps surae followed by an increase in the activity of the ipsilateral tibialis anterior and contralateral erector spinae. This led to a forward-directed force that preceded movement of the arm. This indicates that RP had an essentially normal anticipatory postural activity organized to compensate for the displacement in body center of gravity caused by the upcoming movement of either arm.

Transcranial magnetic stimulation (TMS) of motor cortex

TMS was used to examine the excitability of the corticospinal and corticocortical circuits in the hand area of primary motor cortex (Ridding and Rothwell, 1992). Overall, the STN and GPi lesions have a limited impact on primary motor cortex excitability (Fig. 2C; further details in supplementary material). Treatment with levodopa normalized SICI in the non-operated hemisphere but did not change it in the operated hemisphere (Fig. 2C). The CSP (cortical silent period) was shorter in the non-operated compared with the operated hemisphere (Fig. 2D) ($p<0.05$) which is comparable to the situation in PD where the CSP is shorter than normal (Lefaucheur, 2005).

Functional imaging (fMRI)

Functional imaging was conducted in the "off" medication state. Activation patterns were compared for movements of the right and left hands. Compared to the right hand, movements of the left hand were mainly associated with activation in the right premotor and motor cortices, the left parietal superior lobe and the cerebellum bilaterally (Fig. 4). Compared to the left hand, right hand movements were associated with activation in the left premotor and motor cortices and right parietal superior lobe but the cerebellum was only activated unilaterally on the right side (Fig. 4). Left hand movements, related to the non-operated side of the patient, were associated with notably larger cluster sizes (*k*-scores) in the motor and premotor cortices and cerebellum in comparison with the right (operated) hand movements (Table 2). These findings for the non-operated hemisphere are consistent with previous studies in PD patients (Samuel et al., 1997) in which increased activity of the cerebello-thalamo-cortical loop, compared to normal subjects, has been viewed as compensatory for the dopaminergic deficit.

Temporal discrimination thresholds (TDT)

Left hand TDT was significantly higher than controls (78 ± 17 ms vs. 34 ± 12 ms, mean and SD) and within the range found in a group of mild PD patients in the "off" medication state (78 ± 17 ms vs. 89 ± 22 ms) (Artieda et al., 1992). The TDT value for the right hand was significantly lower than the left hand (58 vs. 78 ms, $p=0.05$) and almost identical to the one found in PD patients in the "on"

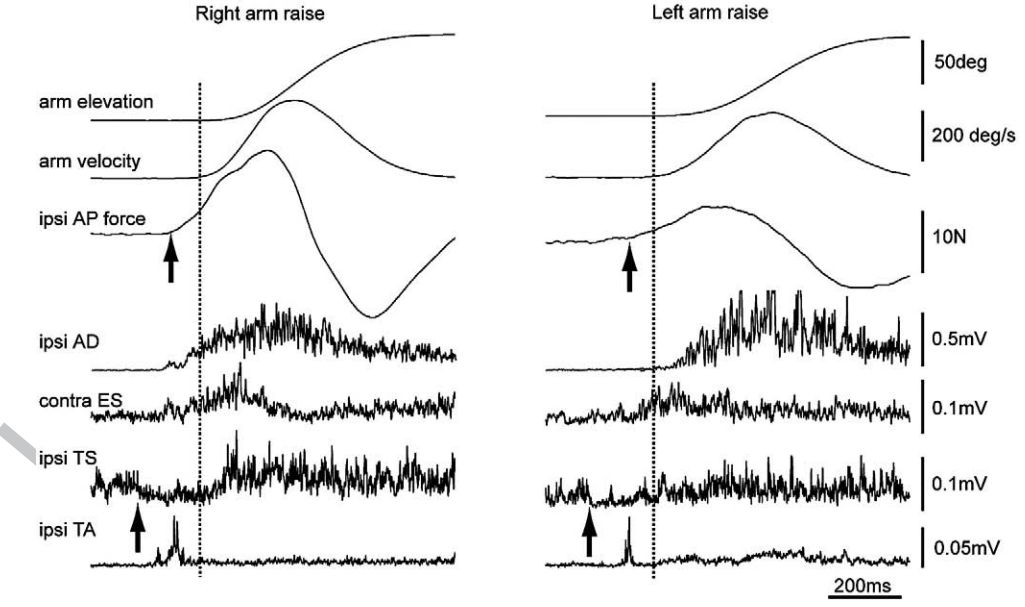

Fig. 3. Postural adjustments during rapid elevation of each arm separately in a normal, age-matched control and patient RP while standing and OFF medication. Traces show averaged movements ($n=8$) after alignment to movement onset (vertical dotted line). Traces depict arm elevation and arm angular velocity in the sagittal plane, and horizontal antero-posterior ground reaction force acting on the foot ipsilateral to the active arm. Bottom four traces show rectified EMG recorded from ipsilateral anterior deltoid (AD; prime mover), contralateral erector spinae (ES), ipsilateral triceps surae (TS) and ipsilateral tibialis anterior (TA). A normal pattern of muscle synergies preceding arm elevation is present on both sides. Note that right arm moves faster than the left.

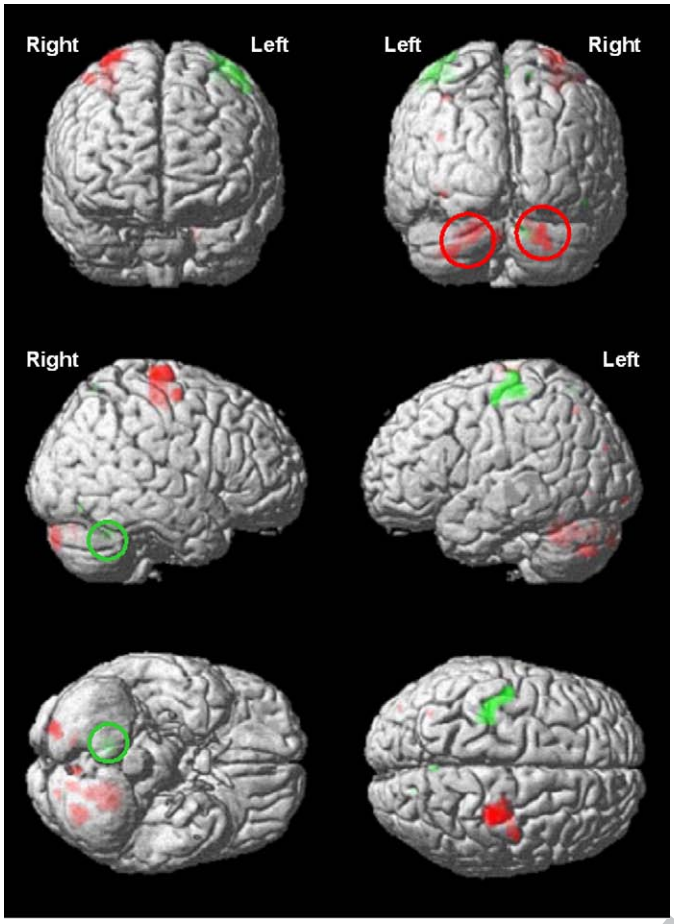

Fig. 4. Functional magnetic resonance imaging associated with left vs. right (red) and right vs. left (green) hand movements of the patient. Activation profiles have been projected on a render SPM single-subject template. Circled regions indicate an important difference regarding the significant ($p<0.05$) activation in the cerebellum, which is bilaterally activated (red) for left ("parkinsonian") hand movements and only ipsilaterally (green) for right ("treated") hand movements. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

medication state (61 ± 15 ms). In the "on" medication state the mean values were 21 and 15 ms for the left and right hand, respectively, indicating normal TDT.

Table 2
Contrasts of cerebral activation sites between left and right hand movements "off" medication.

Region	Side	BA	*Z*-score	*k*	Coordinates
Left hand (parkinsonian side)>right hand (operated side)					
Precentral gyrus, motor cortex	R	4	>8.00	454	24, −27, 62
Precentral gyrus, lateral premotor cortex	R	6	7.24		27, −19, 66
Cerebellum	L		>8.00	390	−22, −56, −31
Cerebellum	R		7.00−6.73	85	19, −89, −29
Parietal superior lobulus	L	7	5.55	6	−31, −65, 39
Occipital gyri	L	18/19	5.69−5.15	2	−36, −73, −8
Right hand (operated side)>left hand (parkinsonian side)					
Precentral gyrus, motor cortex	L	4	7.39	274	−29, −32, 51
Precentral gyrus, lateral premotor cortex	L	6	7.07		−41, −19, 52
Cerebellum	R		7.16	61	10, −56, −30
Parietal superior lobulus	R	7	5.46	10	1, −63, 53
Fusiform gyrus	R	18	5.18	2	41, −73, −15

Z scores correspond to corrected $p<0.05$. BA = Brodmann area; k = cluster size (number of voxels); x, y, z = mediolateral, rostrocaudal and dorsoventral Talairach coordinates. Coordinates have been transformed from MNI to Talairach coordinates.

Tests abnormally performed with the operated limb

Reaction time (RT) tasks

All RT studies were completed in the "on" state. (a) Warned and unwarned simple RT, uncued, partially and fully cued choice RTs: The RTs in RP were similar to those previously reported for patients with mild to moderate PD tested on medication using the same tasks (Jahanshahi et al., 1992) as well as to mean RTs obtained from a meta-analysis of the RT literature in PD (Wang et al., 1998). Simple RTs (mean of warned and unwarned trials) were significantly ($t=2.9$, df = 49, $p=0.006$) faster with the right (mean, 424 ms) than with the left hand (mean, 465 ms) (Fig. 6A, right histogram, and Di). However, there were no other significant differences between the hands in the more complex reaction time tasks with different amounts of advance movement parameter information (uncued, partially and fully cued choice RT) or different intervals between the warning signal/precue and the imperative stimulus (Fig 5). (b) Go/no-go RT task: As in the simple RT task, in the go/no-go reaction task, RTs were faster with the right than the left hand when there were 100% go trials (equivalent to a simple RT task). When the proportion of no-go trials increased, RTs slowed with both hands but the degree of slowing was greater with the right hand (Fig. 5E). This was confirmed in a two-way repeated measures ANOVA of the log transformed RT data with hand (right vs. left) and % go trials (100%, 80%, 50%, 20%) as the within-subject variables. There was a significant interaction between hand × % go trials [$F(3,54)=2.72$, $p=.05$] that was due to the fact that mean RTs with the right hand were significantly faster compared to the left hand with 100% or 80% go trials [$t=-4.83$, df = 48, $p<.0001$; $t=-2.51$, df = 79, $p=.01$, respectively]. In contrast, there was no significant difference in RTs between the right and left hands for the blocks with 50% or 20% go trials. Very few errors were made in the go/no-go task. There were no errors of commission (releasing the home key and pressing the response key on no-go trials) for any of the go/no-go RT conditions for either the right or left hands. There were a number of partial response errors on no-go trials (releasing the home key on no-go trials but without pressing the response key) mainly with the left hand in the 80% (three partial errors) and 50% (one partial error) go trials blocks. For the right hand there was only one partial response error in the 80% go trials block. There were three anticipations (RT <100 ms due to releasing home key before presentation of the go stimulus) on the 100% go trials block with the right hand. The number of anticipations or partial response errors did not differ significantly between the two hands ($p>0.05$).

In summary, these experiments show that RP has faster simple RT with the right, operated hand and he benefited from warning signals and precues to the same extent with both hands. However, the RT advantage for the right hand was lost in a go/no-go RT when the percent of no-go trials in a block increased and the uncertainty about whether to move or inhibit the action increased.

Implicit sequence learning

On the probabilistic serial reaction time task (SRTT), healthy controls have faster mean RTs to the probable targets than to the improbable targets across all blocks (Wilkinson and Jahanshahi, 2007). This results in a positive improbable–probable difference score, the magnitude of which indicates the extent of learning of the sequence (probable trials) across blocks (Fig. 6). Using the same probabilistic SRTT and sequences, we previously found that a group of PD patients demonstrated evidence of probabilistic sequence learning, although learning was significantly attenuated compared to matched healthy controls (Wilkinson and Jahanshahi, 2007; Fig. 6). For both the controls and PD, the RT difference scores were significantly different from zero, indicating learning.

For RP, all assessments were conducted in the "off" state. With his right hand (contralateral to lesion), RP showed an inconsistent RT

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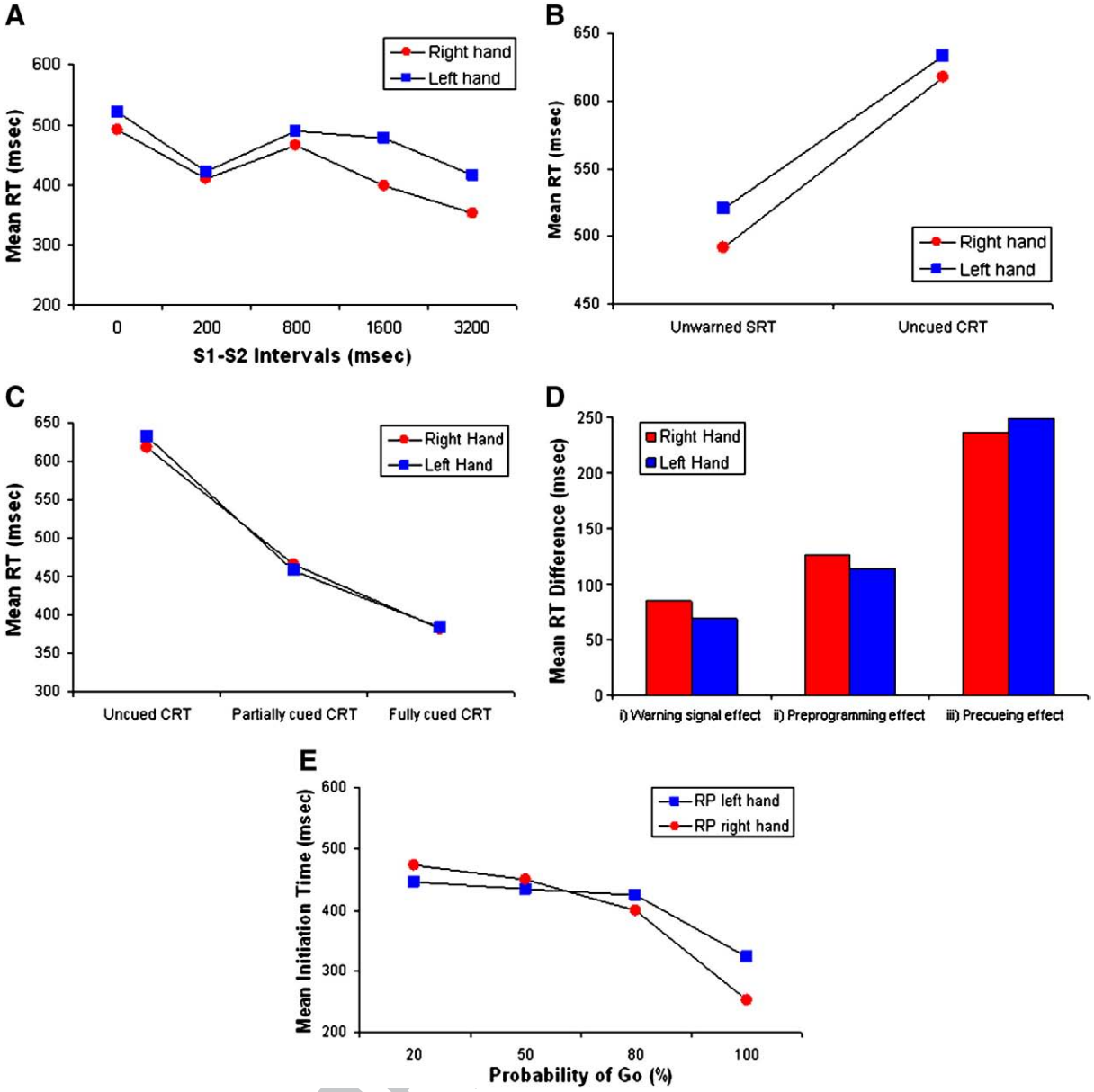

Fig. 5. Reaction times for the simple, uncued, partially precued and fully precued choice reaction time tasks performed with the right and left hands. (A) Unwarned (S1–S2 interval of 0 ms) and warned simple RT for the left and right hands for the S1–S2 intervals. Histogram shown the mean simple RTs (mean of warned and unwarned) for the right and left hands. (B) Mean reaction times for the unwarned simple and uncued choice RT trials for the right and left hands. (C) Mean reaction times for the uncued, partially and fully precued choice RT tasks for the right and left hands. (D) Mean RT difference scores showing the (i) warning signal effect (unwarned minus warned simple RT), (ii) the preprogramming effect (uncued choice RT minus unwarned simple RT) and (iii) the precueing effect (uncued choice RT minus fully precued choice RT) for the right and left hands. (E) Mean reaction times for the right and left hands on the 'go/no-go' reaction time task. Reaction times are plotted as a function of the probability of go trials in a block which varied from 100%, 80%, 50% or 20%.

difference across blocks, despite the fact that his overall RTs were notably faster than those of both the elderly controls and PD patients. The overall RT difference score of 3.7 was not significantly different from zero ($t = -0.33$, $df = 14$, $p = 0.74$), indicating absence of learning with the right hand. In contrast, when performing the task with his left hand, RP showed a larger RT difference score of 12.83, which was similar to that in the PD group. It was marginally different from zero ($t = -1.43$, $df = 14$, $p = 0.09$), and thus indicative of some learning with the left hand as in our previous study of patients with PD.

Additional tests

Other neurophysiological techniques—the Bereitschaftspotential, blink reflex, EEG event related desynchronization, gait initiation and stepping—were assessed but proved unrevealing.

Discussion

The patient described here had evidence of severe striatal dopamine deficiency bilaterally but particularly in the posterolateral region of the left putamen. His initial subthalamotomy led to sustained and disabling dyskinesias of the right arm. However, these were abolished by a subsequent posteroventral pallidotomy on the same side, which abolished the dyskinesias while sustained the clinical benefit to movements on the right side. Thus, the combined lesion of GPi and STN in this patient effectively removed the vast majority of the anatomical output of the BG to the motor thalamocortical projection (Fig. 1A) regarding movements of the right limbs, and the arm in particular. Yet, the patient's right limb movements were substantially improved and he was able to perform normally a large number of daily life motor activities even when in the "off"

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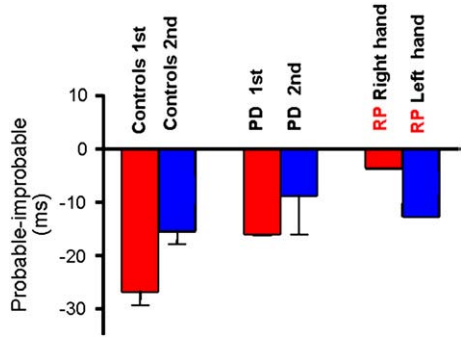

Fig. 6. Implicit sequence learning on the probabilistic serial reaction time task. The data shown are mean differences in reaction times to probable and improbable targets for RP's right and left hands. Also shown are the RT difference scores for healthy controls and patients with PD performing two parallel sequences with the right hand in the study of Wilkinson and Jahanshahi (2006).

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condition. The results presented have some limitations that require brief initial discussion.

First is the question of what additional insight the current double STN and GPi lesion adds over and above that of a simple pallidotomy. Pallidotomy, as typically performed for patients with PD, had a drastic effect against levodopa-induced dyskinesias but only a modest effect against parkinsonian motor features. Patients also continue to respond well to levodopa (Fine et al., 2000) suggesting that pallidotomy does not block completely the motor circuit. In our patient and in the related series of similar patients we have assessed clinically, subthalamotomy carried a marked anti-parkinsonian benefit, while the subsequent pallidotomy abolished the hemichorea-ballism with a lesion that was likely placed in the GPi motor region. In this case levodopa produced only a small clinical improvement and had no effect on some physiological tests. Altogether, this may be taken to indicate that the combined lesions had a profound effect in interrupting BG output in the motor circuit. The second limitation concerns the validity of an $n=1$ observation. In an ideal situation we would have liked to study in detail more of the other patients in the present series with STN + GPi lesions. However, since the patients were operated in a different country (i.e., Cuba) to where the tests could be performed (i.e., England and Spain), this proved to be logistically impossible. Nevertheless, we would argue that the present study fulfills the established requirements for $n=1$ report (Shadmehr and Krakauer, 2008). Thus, we found impairment in specific tasks, namely, implicit sequence learning and the go/no-go RT task, which coupled with the normal performance in many other motor tasks constitute dissociation. An additional hand-specific dissociation was also evident since our patient had a learning capability similar to that of average PD patients with the left hand but was more impaired with the right hand; similarly, in the go/no-go task the right hand superiority over the left was lost when the % go signals was reduced. Finally, the lesions were made on the left hemisphere and we cannot be certain about the impact of similar lesions on the right basal ganglia. However, we evaluated clinically a few patients ($n=3$) with left HCB after right side subthalamotomy who required pallidotomy and their motor performance was identical to the described here for patient RP.

Functions which were improved or spared

The clinical impression of a marked improvement of speed of movement initiation and execution with the right hand contralateral to the surgical lesions was confirmed in several tests, such as the performance of simultaneous hand movements, in the simple RT task and the associated pattern of brain activation (fMRI). There also was improvement of a non-motor test of temporal discrimination, a task that requires temporal processing and activation of the BG (Jahanshahi et al., 2006; Rao et al., 2001). All these effects may be interpreted as the result of liberating the cortex from excessive inhibition and/or background neural "noise," which in the parkinsonian state may interfere with movement initiation and execution as well as sensory processing (Obeso et al., 1997; Lozano et al., 2000; Vitek and Giroux, 2000; Levy et al., 2002; Buhusi and Meck, 2005). These findings are consistent with previous reports in PD patients who underwent either pallidotomy or subthalamotomy (Samuel et al., 1997; Limousin et al., 1999; Levy et al., 2002; Brown et al., 2003; Trost et al., 2006) and current modelling of the BG in PD (Rubchinsky et al., 2003). Interestingly, levodopa induced a modest clinical improvement in the right limbs which was also paralleled by mild increase in movement speed in the simultaneous flex and squeeze task, but no change in motor cortex excitability of the left hemisphere. This might imply that the mechanism of action of levodopa in PD is not entirely mediated by the striato-pallidal connections within the motor circuit of that hemisphere. One possibility is that part of the anti-parkinsonian effect of levodopa could be mediated through striato-SNr (substantia nigra pars reticulata)-thalamic projections. Certainly, SNr neuronal activity is abnormal in the parkinsonian state (Wichmann et al., 2001) and it is modulated by levodopa (probably by D-1 receptor activation) in the MPTP monkey model (Vila et al., 1996; Kliem et al., 2007) and PD patients (Prescott et al., 2009). Moreover, in MPTP monkeys subthalamotomy induces a marked reduction of SNr hyperactivity (Guridi et al., 1996). However, SNr is not primarily engaged in movement control of the upper limb (Wichmann and Kliem, 2004). Other, not exclusive, explanations may be that a more complete restoration of DA deficiency improves associative and limbic circuits which were probably not completely interrupted in the operated hemisphere. There is also a possible involvement of the non-operated hemisphere since there is anatomical evidence for corticocortical (Pandya and Vignolo, 1971) and bilateral cortico-BG (Parent and Hazrati, 1995; Tokuno et al., 1999) connectivity and imaging studies often show bilateral cortical (Hanakawa et al., 2005) and BG activation (Lehericy et al., 2005) during movement of a limb. In the "off" parkinsonian state there is a loss of specificity in motor cortical areas in response to peripheral stimuli (Escola et al., 2003). Thus, it is conceivable that in patient RP, despite the general normalization of motor mechanisms induced by surgery, the left hemisphere could be perturbed and impaired by abnormal input signals, leading to sub-normal performance in some tasks.

Q5

The broad spectrum of movements and activities that were unimpaired in patient RP could be interpreted as the result of plastic functional changes or the recruitment of alternative pathways as shown to occur regarding learning in PD patients (Beauchamp et al., 2008). Thus, it could be argued that the chronically dysfunctional parkinsonian brain might have adapted to abnormal BG output activity and re-organized thalamo-cortical motor mechanisms to operate without such input (Aparicio et al., 2005). Consequently, a surgical lesion of the BG output circuitries would not be expected to have a negative effect. We believe this is unlikely. PD patients on long-standing treatment with levodopa, like RP, dramatically alternate several times per day from periods with excellent, even normal, mobility to severely reduced movement capacity associated with rigidity, tremor and other parkinsonian manifestations. BG output is also known to change from increased neuronal firing and bursting activity as well as higher synchronization in the beta band during the "off" periods to reduced firing rate and predominance of the gamma and theta bands in the "on" motor state (Papa et al., 1999; Vitek and Giroux, 2000; Brown, 2003; Brown et al., 2003; Alonso-Frech et al., 2006). It is difficult to accept that such drastic behavioral and neurophysiological changes, repeatedly occurring several times per day, could be gated out by the motor system. In addition, BG surgery (pallidotomy, subthalamotomy and DBS) is associated with a very rapid motor improvement, taking place sometimes within the operating room, and significant reactivation of motor cortical areas

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(dorsolateral prefrontal cortex, supplementary motor area (SMA), areas 6 and 4 (Ceballos-Baumann et al., 1994; Samuel et al., 1997; Limousin et al., 1999; Asanuma et al., 2006)). Thus, all available evidence suggests that the cortex is actively and continuously influenced by abnormal BG input in PD. Interrupting BG output removes such abnormal signaling and allows the motor system to operate more normally.

Motor control of the limbs is primarily mediated by the motor loop (DeLong et al., 1986) which was to a large extent disrupted by the dopaminergic deficit and the surgical lesions. It is possible that other striato-pallidal projections, corresponding to associative and limbic loops, could compensate for the interruption of the motor loop. It could also be that SNr output could take over motor control of the limbs. We cannot ruled out completely either possibility but do not think these are likely. Thus, compensation of neurological deficits typically occurs over weeks or months and our patients exhibited no clinical movement defect at any time after pallidotomy and the SNr is scarcely activated by movements of the limbs in monkeys (Wichmann et al., 2001) and PD patients (Rodriguez-Oroz et al., 2001).

Abnormal functions

Despite RP's excellent functioning and use of the right hand in daily life activities, there were two tasks in which performance worsened considerably in the right hand. In the go/no-go task, the performance with the right hand lost its speed advantage over the left hand when the percent of no-go trials and hence action uncertainty increased. Thus, right hand RTs were significantly faster than the left with 100% go trials, but this advantage disappeared when the percent of go trials in a block was reduced to 50% and 20%. In addition, although learning was somewhat compromised in the SRTT task with the left hand (as expected in patients with Parkinson's disease) there was a striking lack of implicit sequence learning with the right hand even though the overall reaction times were much faster with the right than the left.

These go/no-go and SRTT tasks have two features in common. First, performance of either task depends on the integrity and interaction of frontal-BG connections. Second, they share a probabilistic nature. The SRTT is commonly used to study implicit sequence learning (Nissen and Bullemer, 1987; Wilkinson and Jahanshahi, 2007). A wealth of imaging studies in normal people (Grafton et al., 1995; Hazeltine et al., 1997; Peigneux et al., 2000) and clinical evidence (Beauchamp et al., 2008; Doyon et al., 1997; Jackson et al., 1995; Kelly et al., 2004; Wilkinson and Jahanshahi, 2007) indicate that the striatum plays a critical role in implicit sequence learning. Indeed, SRTT is known to be attenuated in PD (Jackson et al., 1995; Kelly et al., 2004; Siegert et al., 2006; Wilkinson and Jahanshahi, 2007) and further impaired after pallidotomy (Brown et al., 2003). Our results provide strong support for a key role of the BG in implicit motor sequence learning.

Performance of go/no-go tasks engages the dorsolateral, inferior or orbitofrontal areas as established by animal studies (Iversen and Mishkin, 1970; Sasaki and Gemba, 1986), clinical observations (Leimkuhler and Mesulam, 1985) and functional imaging studies (Konishi et al., 1999; Garavan et al., 2002). The go/no-go task depends on a balance between preparing for execution of the response on go trials, while simultaneously preventing release of the response on no-go trials. The RT data indicate that motor preparation is reduced when the go trials are less frequent and the response is more likely to be inhibited. There is a wealth of evidence for BG involvement in both these aspects of the task. Animal (Aldridge, Thompson and Gilman, 1997) and imaging studies in humans (Aron et al., 2003; Kelly et al., 2004, Liston et al., 2006) show BG involvement in tasks requiring response inhibition (Aron and Poldrack, 2006; Aron et al., 2003; Liston et al., 2006). In addition there is evidence that the striatum is engaged during various types of probabilistic learning (Poldrack et al., 2001; Balleine et al., 2007) and that the degree of uncertainty in decision making correlates negatively with striatal activity (Hsu et al., 2005). The context of uncertainty, whether transitioning from high to low probability or the reverse, modulates the striatal response (Bischoff-Grethe et al., 2001). We conclude that either or both of these functions, suppression of a prepared response and probabilistic preparation and selection of the appropriate response are essential features of the BG contribution to cortical processing underlying fine motor tasks in humans (Gurney et al., 2001) that are missing in the left hemisphere of patient RP.

A fundamental paradox of the classic BG model was that surgical lesions of the GPi or motor thalamus in PD are not generally associated with any major and persistent motor disturbance (Laitinen and Vilkki, 1973) or with worsening of parkinsonian features (Hassler et al., 1960; Kelly and Gillingham, 1980; Mundinger et al., 1970). The effect of focal GPi lesion or inactivation (with muscimol) in monkeys is somehow variable (Mink, 1996; Wichmann and DeLong, 1996) but most studies have found reduced amplitude and slowing of movement and dystonic features of the upper limb (Mink and Thach, 1991; Wenger et al., 1999; Desmurget and Turner, 2008). On the other hand, these anomalies are mild and not associated with any major defect in motor control (Inase et al., 1996; Buford et al., 1996), so that accuracy of reaching movements and rapid sequential movements of the hand were preserved as well as the ability to stop a wrongly initiated movement (Desmurget and Turner, 2008). In keeping with these experimental data, here we show that the BG–cortical connections cannot be interrupted in a human with complete impunity. The associated abnormalities may be too subtle to be noticeable or detectable in routine behaviors, explaining the overall clinical improvement seen in PD patients after surgery and the scarcity of clinical manifestations in people with focal BG lesions (Bhatia and Marsden, 1994; Marsden and Obeso, 1994; Aparicio et al., 2005). Our results also support the prediction that surgical lesions of the BG in PD would be associated with inflexibility or reduced capability for motor learning (Marsden and Obeso, 1994).

Conclusions

Movements of the upper limb are primarily mediated by the cortico-putaminal-pallido-thalamo-cortical motor loop (DeLong et al., 1986). Our results show that derangement of major components of such motor loop probably causing interruption of BG motor output to the thalamo-cortical projection unilaterally does not interfere with routine operations but impairs tasks which require facilitation of appropriate responses in a probabilistic context (SRTT and go/no-go tasks in our study). Accordingly, once a movement or task is learned the BG is not necessary for its execution. Abnormal BG neuronal activity, as in PD, leads to greater motor abnormality than when its output is silenced or eliminated. These findings explain the overall beneficial clinical effect of surgery in PD but also reveal that the BG is needed under some novel circumstances to learn, move and act normally. This resolves the paradoxical observation from early studies indicating that BG output in humans could be disrupted without an apparent deficit. A final practical consideration is that our observation indicates that the risk of persistent dyskinesias needs not be viewed as a contraindication to subthalamotomy when circumstantially needed. Pallidotomy readily eliminates hemichorea-ballism in PD without producing deficits that have practical consequences for daily life. This confirms the view (Marsden and Obeso, 1994; Lozano et al., 2000) that it is better to dispense with BG output than having a faulty one.

Uncited reference

Albin et al., 1995

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.expneurol.2009.08.030.

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