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From off-period dystonia to peak-dose chorea
The clinical spectrum of varying subthalamic nucleus activity

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Summary
The effect of chronic bilateral high-frequency stimulation of the subthalamic nucleus (STN) on levodopa-induced dyskinaesias was investigated in eight patients with fluctuating Parkinson's disease complicated by functionally disabling off-period dystonia. All of the patients also had severe diphasic and peak-dose chorea, so that it was possible to study the effect of high-frequency stimulation on the different types of levodopa-induced dyskinaesias. Off-period fixed dystonia was reduced by 90% and off-period pain by 66%. After acute levodopa challenge, high-frequency stimulation of the STN reduced diphasic mobile dystonia by 50% and peak-dose choreic dyskinaesias by 30%. The effect of bilateral high-frequency stimulation of the STN on the Unified Parkinson's Disease Rating Scale motor score had the same magnitude as the preoperative effect of levodopa. This allowed the levodopa dose to be reduced by 47%. The combination of reduced medication and continuous high-frequency stimulation of the STN reduced the duration of on-period diphasic and peak-dose dyskinaesias by 52% and the intensity by 68%. Acute high-frequency stimulation of the STN mimics an acute levodopa challenge, concerning both parkinsonism and dyskinaesias, and suppresses off-period dystonia. Increasing the voltage can induce repetitive dystonic dyskinaesias, mimicking diphasic levodopa-induced dyskinaesias. A further increase in voltage leads to a shift from a diphasic-pattern dystonia to a peak-dose pattern choreodystonia. Chronic high-frequency stimulation of the STN also mimics the benefit of levodopa on parkinsonism and improves all kinds of levodopa-induced dyskinaesias to varying degrees. Off-period dystonia, associated with neuronal hyperactivity in the STN is directly affected by stimulation and disappears immediately. The effect of chronic high-frequency stimulation of the STN on diphasic and peak-dose dyskinaesias is more complex and is related directly to the functional inhibition of the STN and indirectly to the replacement of the pulsatile dopaminergic stimulation by continuous functional inhibition of the STN. Chronic high-frequency stimulation of the STN allows a very gradual increase in stimulation parameters with increasing beneficial effect on parkinsonism while reducing the threshold for the elicitation of stimulation-induced dyskinaesias. In parallel with improvement of parkinsonism, the levodopa dose can be gradually decreased. As diphasic dystonic dyskinaesias are improved to a greater degree than peak-dose dyskinaesias, both direct and indirect mechanisms may be involved. Peak-dose choreatic dyskinaesias, associated with little evidence of parkinsonism and thus with low neuronal activity in the STN, are improved, mostly indirectly. Fixed off-period dystonia, mobile diphasic dystonia and peak-dose choreodystonia seem to represent a continuous clinical spectrum reflecting a continuous spectrum of underlying activity patterns of STN neurons.

Keywords: Parkinson's disease; levodopa-induced dyskinaesias; dystonia; subthalamic nucleus; deep brain stimulation

Abbreviations: GPi = globus pallidus internus; HFS = high-frequency stimulation; LID = levodopa-induced dyskinaesias; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction
Dystonia in Parkinson's disease was well known in the pre-levodopa era. Charcot (Charcot, 1892) described the typical fixed deformities of the hands and feet in Parkinson's disease patients with advanced disease. Stewart described intermittent exertion-induced dystonia of the foot as an early symptom of Parkinson's disease a century ago (Stewart, 1898).

Approximately a quarter to a third of the patients managed before the levodopa era may have eventually developed hand and foot dystonia (Marsden *et al*., 1982). In the first reports of chronic levodopa therapy, dyskinaesias were recognized as a complication (Cotzias, 1967, 1969; Barbeau, 1969, 1971, 1975; Yahr *et al*., 1969). The semiology of levodopa-induced dyskinaesias (LID) varies with the clinical fluctuations of parkinsonism, largely reflecting plasma concentrations of levodopa (Fahn, 1982). As with on–off response variations, they become more severe with progression of the disease and increasing drug dosage. According to the levodopa plasma concentrations, LID are classified into off-period, diphasic and peak-dose dyskinaesias.

Off-period dystonia typically presents as fixed dystonic postures, diphasic dyskinaesias as mobile dystonia, and peak-dose dyskinaesias as mixed chorea and dystonia (choreodystonia) or as chorea. Chronic levodopa therapy may accentuate the characteristic dystonic toe and foot posturing in patients with Parkinson's disease (Duvoisin *et al*., 1972). Foot dystonia appears in the off-period with low plasma levodopa concentrations (McHale *et al*., 1990), typically in the early morning on awakening, before the first dose of levodopa (Lees *et al*., 1977; Melamed, 1979; Poewe and Lees, 1987; Poewe *et al*., 1988). Off-period dystonia may completely disappear if levodopa is withdrawn for a few days (Melamed, 1979; Ilson *et al*., 1984; Poewe *et al*., 1988). One-third of the patients with idiopathic Parkinson's disease on chronic medical treatment suffer from debilitating, painful foot dystonia (Nausieda *et al*., 1980). Off-period dystonia is more frequent in patients with young-onset Parkinson's disease (Quinn *et al*., 1987; Gibb and Lees, 1988), especially those with severe akinesia and a good levodopa response (Agid *et al*., 1979). There is a strong association between pain and dystonia in Parkinson's disease (Quinn *et al*., 1986).

Diphasic dyskinaesias appear at the beginning and at the end of the levodopa effect, when parkinsonism is present, while blood concentrations of levodopa are increasing or decreasing (Tolosa *et al*., 1975; Barbeau, 1976; Muenter *et al*., 1977; Lees *et al*., 1977; Lhermitte *et al*., 1977; Agid *et al*., 1985). They typically present as slow, stereotyped, repetitive movements (Marsden *et al*., 1982) due to alternating contraction of antagonist muscles (Luquin *et al*., 1992) and may be accompanied by a worsening of tremor (Barbeau, 1975) and akinesia (Merello and Lees, 1992). They usually begin distally in the lower limbs during the transition from the off to the on state and spread in an ascending wave to the trunk and the upper limbs (Marconi *et al*., 1994). They are generally qualified as dystonic, but if the hips or shoulders are involved the amplitude of the movements may become so great that the violent flailing of the limbs resembles ballism (Marsden *et al*., 1982; Luquin *et al*., 1992). Such episodes can be extremely painful and occur with mental anguish and autonomic changes (Barbeau, 1975; Marsden *et al*., 1982). An increase in dopaminergic stimulation may improve diphasic dyskinaesias in the short term (Lhermitte *et al*., 1977; de Saint Victor *et al*., 1992). End-of-dose dyskinaesias tend to be more severe than beginning-of-dose dyskinaesias. Diphasic dyskinaesias during the day tend to be more severe than after the first dose of levodopa in the morning. Towards the end of the day, severe and long-lasting crises of diphasic dyskinaesias may represent a therapeutic challenge (Zimmerman *et al*., 1994). Diphasic dyskinaesias are less common than peak-dose dyskinesia (Barbeau, 1975) and typically present in young patients with severe akinesia and a good levodopa response (Lhermitte *et al*., 1977).

Peak-dose dyskinaesias (Barbeau, 1975; Lees *et al*., 1977) occur at the peak of benefit following the administration of levodopa, when patients are hypotonic and show only minimal signs of parkinsonism, and plasma levodopa levels are above a certain critical individual concentration (Muenter *et al*., 1977; Agid *et al*., 1985). An increase in levodopa dosage worsens peak-dose dyskinaesias. They most commonly affect the upper part of the body, especially the face, the neck and the trunk, but they tend to be generalized, the upper limbs being more severely involved than the lower limbs (Luquin *et al*., 1992; Marconi *et al*., 1994). They are predominantly choreic in nature but may also show dystonic features (Marsden *et al*., 1982). The occurrence of dyskinaesias depends on the degree of dopaminergic denervation (Blanchet *et al*., 1996). In patients with severe akinesia, 50% developed peak-dose dyskinaesias after 2 months and 90% after 3 years of treatment with levodopa (Barbeau, 1975). In patients with Hoehn and Yahr stage I or II at the initiation of levodopa treatment, the incidence of dyskinaesias after 3 years was 56% (Blanchet *et al*., 1996). In the DATATOP study (Parkinson Study Group, 1996) patients also had less severe parkinsonism when levodopa was initiated [Hoehn and Yahr stage <2 and motor Unified Parkinson's Disease Rating Scale (UPDRS) approximately 20/108 on average]. Thirty per cent developed dyskinaesias after 12 months of levodopa (plus peripheral decarboxylase inhibitor with or without deprenyl) treatment. Patients developing dyskinaesias were being treated with 387 ± 169 mg levodopa whereas a matched set of patients who did not develop dyskinaesias were receiving a lower daily dose of levodopa.

Levodopa-induced off-period dystonia as well as diphasic dyskinaesias constitute a pharmacological paradox, being caused and relieved by the same agent (Poewe and Lees, 1987; de Saint Victor *et al*., 1992). The mechanisms underlying the different types of dyskinaesias remain largely unknown. Striatal cholinergic hyperfunction and a functional dopaminergic deficit, possibly involving only one subclass of dopamine receptors, have been proposed as the underlying mechanisms of foot dystonia in parkinsonism (Parkes *et al*., 1976; Lees *et al*., 1977; Agid *et al*., 1979, 1985; Poewe and Lees, 1987). The different classes of dopamine receptors, as well as other neurotransmitters, have been proposed to be involved in the pathophysiology of on-period dyskinaesias (Mouradian *et al*., 1989; Bedard *et al*., 1992; Blanchet *et al*., 1995; Chase *et al*., 1996; Grondin *et al*., 1996; Goulet *et al*., 1997; Verhagen Metman *et al*., 1998). Dyskinesias require denervation of the nigrostriatal system in the presence of an

intact striatal outflow (Schneider, 1989; Boyce *et al*., 1990). Levodopa does not induce dyskinaesias in humans who do not have Parkinson's disease (Mones *et al*., 1971; Nutt and Holford, 1996). Dyskinesias usually appear first on the most affected side in asymmetrical parkinsonism, indicating that they are related to the severity of dopaminergic denervation (Mones *et al*., 1971). Dyskinesias are more frequent in patients with severe central dopaminergic depletion (Agid *et al*., 1979; Horstink *et al*., 1990) and with a good levodopa response (Mones *et al*., 1971). In monkeys with parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), dopaminergic agents induce dyskinaesias only in those with >95% dopaminergic depletion (Schneider, 1989). The severity of disease at levodopa initiation seems to be a more significant risk factor for LID than the duration of levodopa treatment itself (Bergmann *et al*., 1987; Blin *et al*., 1988; Cedarbaum *et al*., 1991; Blanchet *et al*., 1996). The development of dyskinaesias also requires repeated dopaminergic therapy; the first exposure to levodopa does not induce dyskinaesias (Mones *et al*., 1971; Nutt and Holford, 1996). The fluctuations of synaptic dopamine inherent in the usual oral treatment of Parkinson's disease might result in deleterious postsynaptic changes (Sage and Mark, 1992). Continuous dopaminergic therapy can decrease dyskinaesias induced by pulsatile stimulation of the dopamine receptors (Mouradian *et al*., 1990; Schuh and Bennett, 1993; Blanchet *et al*., 1995; Colzi *et al*., 1998; Syed *et al*., 1998).

In the pre-levodopa era, rigid dystonic deformities in advanced Parkinson's disease were noted to completely disappear after occlusion of the anterior choroidal artery (Cooper, 1954). Pallidal surgery improves symptomatic hemiballism or hemichorea (Talairach *et al*., 1950; Guiot and Brion, 1952; Gioino *et al*., 1966). Pallidotomy (Laitinen *et al*., 1992; Dogali *et al*., 1995; Lozano *et al*., 1995; Baron *et al*., 1996) and pallidal high-frequency stimulation (HFS) (Siegfried and Lippitz, 1994; Krack *et al*., 1998*a*) have been reported to directly improve all types of LID. Lesioning the pallidal terminal territory within the thalamus (Narabayashi *et al*., 1984; Page *et al*., 1993) and thalamic HFS (Caparros Lefebvre *et al*., 1993) also alleviate LID. In the first patients subjected to HFS of the subthalamic nucleus (STN), off-period dystonia was noted to disappear completely as a direct consequence of HFS (Limousin *et al*., 1995). Acute HFS of the STN using high stimulation parameters can induce dyskinaesias (Mundinger, 1965; Limousin *et al*., 1996) in the same way as STN lesions (Martin, 1927).

Since HFS is known to reproduce the effects of a lesion in the ventro-intermediate thalamic nucleus (Benabid *et al*., 1991, 1996), we initially thought that patients with marked diphasic or peak-dose dyskinaesias would be particularly at risk of developing dyskinaesias with STN HFS. For this reason the presence of disabling dyskinaesias was initially an exclusion criterion for STN HFS. As globus pallidus internus (GPi) HFS was less effective on akinesia than STN HFS in our experience, we gradually selected patients with increasing disability related to dyskinaesias for STN HFS (Krack *et al*., 1998*b*). Surprisingly, long-term STN HFS also improved peak-dose dyskinaesias (Krack *et al*., 1997; Limousin *et al*., 1998). In the present paper, we investigated the effects of STN HFS on off-period dystonia, diphasic dyskinaesias and peak-dose dyskinaesias in Parkinson's disease patients with severe motor complications. The primary intention was to study the effect of STN HFS on off-period dystonia, and patients with disabling off-period dystonia were selected. We found that chronic STN HFS improved all types of LID to a varying degree, the most dramatic effect being on off-period dystonia. These observations provide some insight into the pathophysiology of LID.

Patients and methods

A series of 27 consecutive patients underwent surgery for bilateral STN HFS, according to a procedure previously described (Limousin *et al*., 1995). All the patients had fluctuating idiopathic Parkinson's disease. A levodopa challenge was carried out twice before surgery following a 12-h overnight withdrawal of dopaminergic treatment. A suprathreshold dose (Krack *et al*., 1998*b*), exceeding the usual morning dose by 50–100 mg of levodopa, plus a peripheral decarboxylase inhibitor was given. The UPDRS (Fahn and Elton, 1987) was rated in the on- and off-drug conditions.

At the 6-month follow-up, a levodopa test using the same dose as preoperatively was carried out. UPDRS scores were rated in off-drug/off-stimulation, off-drug/on-stimulation, on-drug/off-stimulation and on-drug/on-stimulation conditions on the same day. Whereas the evaluation always started with the off-drug condition, the order of the stimulation condition was randomized. In each drug condition, the stimulation condition was changed after the motor evaluation, including the motor score of the UPDRS and timed tests (results of timed tests are not shown in this paper), lasting up to 30 min. After a change in the stimulation condition, we waited at least 10 min before assessing the new condition. In addition to the standardized evaluation, overnight stimulation withdrawal was done only exceptionally, if tolerated by the patient. Patients were videotaped during the entire levodopa test, including the timed tests of the core assessment programme for intracerebral transplantation (Langston *et al*., 1992), and were blinded to the stimulation condition. Off-period, diphasic and peak-dose dyskinaesias were rated by a non-blinded investigator from the video recordings of the levodopa test before surgery and 6 months after surgery in the on-stimulation condition. The intensity of dyskinaesias was rated separately for the face, neck, trunk and each of the upper and lower limbs (Marconi *et al*., 1994). The most severe off-period, diphasic and peak-dose dyskinaesias observed during the whole period of motor evaluation were rated for each limb separately. As dyskinaesias were rated continuously from the video recordings, repeated evaluation was possible whenever necessary. The activation modes used were speaking and the movements performed during both UPDRS

Table 1 *General characteristics of the patients at the time of surgery*

Patient	Sex	Age at onset (years)	Duration of disease (years)	Levodopa equivalent (mg/day)	Hoehn and Yahr off drug	Hoehn and Yahr on drug
1	M	40	8	2000	5	2
2	M	36	14	1700	4	2
3	M	35	15	1150	5	3
4	F	48	12	1150	4–5	3
5	M	36	8	1000	4–5	0
6	F	30	12	2000	5	2.5
7	F	46	18	1700	5	3
8	F	29	16	1200	5	2.5
Mean ± SD		38 ± 7	13 ± 4	1490 ± 410		

examination and timed tests, including walking and hand-tapping. During these tasks, the wording of a dyskinesia severity rating scale (Goetz *et al*., 1994) was used as a guide: 0, absent; 1, minimal severity, no interference with voluntary motor acts; 2, dyskinaesias may impair voluntary movements but the patient is normally capable of undertaking most motor acts; 3, intense interference with movement control and (daily life) activities are greatly limited; 4, violent dyskinaesias, incompatible with any normal motor task (in the body part affected). To increase the sensitivity and to allow distinction to be made between dyskinaesias being present only intermittently on activation or spontaneously all the time, half-points were allowed. Global off-period, diphasic and peak-dose scores were calculated by addition of the subscores from the different body parts, the maximal global score being 28. As the main objective was to analyse and document the effect of STN HFS on dystonia, we selected all those patients from the consecutive series who had an off-period dystonia rating of $\geqslant 3$ in at least one limb. Dystonic postures in the off-period were considered as off-period dystonia. Stereotyped, rhythmic, repetitive dystonic (as well as occasional more clonic, choreodystonic or ballistic) movements (Luquin *et al*., 1992) during the transition periods between off-drug and on-drug motor states were considered as diphasic-pattern dyskinaesias. Choreodystonic, choreic or ballistic movements during the maximal effect of levodopa on parkinsonian signs were considered as peak-dose dyskinaesias.

The characteristics of the patients are summarized in Table 1. The levodopa-equivalent dose was calculated on the basis of the following correspondences adapted from Lozano and colleagues (Lozano *et al.*, 1995): 1 mg pergolide = 1 mg lisuride = 10 mg bromocriptine = 10 mg apomorphine = 100 mg levodopa + dopa decarboxylase inhibitor. After surgery the drug dose was decreased according to the improvement in parkinsonism induced by STN HFS. The study received the approval of the Grenoble University Hospital ethical committee and all patients gave their informed consent. The complete results on parkinsonian signs and symptoms have been presented elsewhere (Limousin *et al*., 1998). The two preoperative subscores of the UPDRS and of LID were averaged. Pairwise comparisons between the results of the mean of the preoperative and postoperative evaluations were made with the Wilcoxon signed rank test. Preoperative and postoperative drug dosages were compared using Student's *t* test.

Results

In a series of 27 consecutive patients who underwent bilateral STN surgery for Parkinson's disease with on–off fluctuations, eight suffered severe off-period dystonia preoperatively, with a rating of at least 3 in at least one limb. The drug changes, stimulation parameters, motor evaluation, off-period dystonia, diphasic dyskinaesias, peak-dose dyskinaesias, subjective changes in pain and the duration and intensity of dyskinaesias in these eight patients at the 6-month follow-up on chronic STN HFS are presented. The levodopa-equivalent dose was reduced by 47% from 1488 ± 408 mg/day preoperatively to 786 ± 445 mg/day postoperatively ($P < 0.01$). Monopolar bilateral HFS was used continuously in all the patients. The average voltage used was 2.5 ± 0.6 V. The frequency was 130–185 Hz and the pulse width 60 μs for all patients. The effect of bilateral STN HFS on the motor score of the UPDRS is shown in Fig. 1. A striking similarity between the effects of STN HFS and levodopa is seen. On average, the motor score improved by 74% (from 63.4 ± 9.8 to 16.6 ± 9.0) in the preoperative levodopa challenge and by 71% (to 18.3 ± 9.7) under bilateral STN HFS in the off-drug condition. Bilateral STN HFS reduced the severity of off-period dystonia by 90% (Fig. 2). During the levodopa challenge, using the same suprathreshold dose as before the operation, the severity of diphasic dyskinaesias was reduced by 50% ($P < 0.05$) and that of peak-dose dyskinaesias by 30% ($P < 0.05$) (Fig. 2).

All of the patients with severe dystonia suffered from severe off-period pain preoperatively. Pain in the off-period (UPDRS item 17) decreased by 66% (from 3.8 ± 1.3 to 1.3 ± 0.9; $P < 0.05$). It was improved in all the patients except one complaining of off-period dopa-sensitive abdominal pain without visible muscular contraction. Duration (UPDRS item 32) of the on-period dyskinaesias (diphasic and peak-dose) decreased by 52% (from 2.3 ± 0.9 to 1.1 ± 0.4; $P < 0.05$) and disability related to on-period dyskinaesias (UPDRS item 33) decreased by 68% (from 2.5 ± 1.2 to 0.8 ± 0.9; $P < 0.05$).

Side effects were minimal. One patient developed a

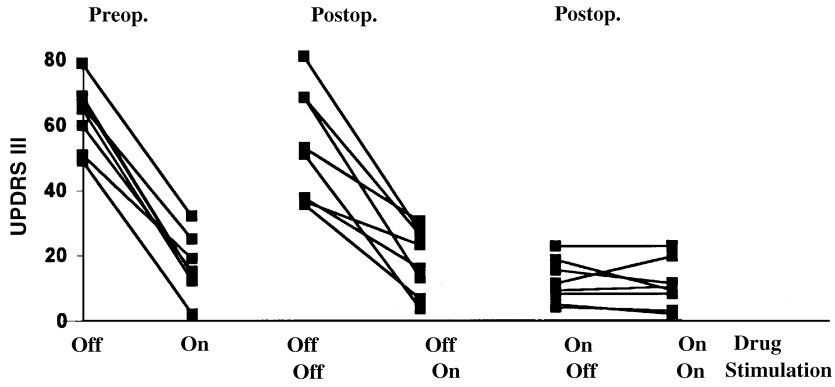

Fig. 1 Preoperative effect of levodopa on the motor Dyskinaesia score of the UPDRS (left), the postoperative effect of bilateral STN HFS (middle) and the postoperative effect of levodopa and of levodopa plus stimulation (right) in eight patients. The effect of STN HFS is very close to the preoperative levodopa effect.

subcutaneous infection at the site of the extension lead. The extension and the stimulator on that side were removed, and the patient was treated with antibiotics. The device was re-implanted after 6 months and the follow-up took place 6 months after the second implantation. All of the patients gained weight following surgery (3.6 ± 1.2 kg).

In order to illustrate the characteristics of LID in young and highly dopa-sensitive patients with severe Parkinson's disease complicated by on–off fluctuations, as well as the effects of acute and chronic STN HFS on the different types of dyskinaesias, we report in detail the semiology of off-period, diphasic and peak-dose dyskinaesias before and after surgery. Detailed results are given for three typical patients and a summary of the findings in all the patients is provided.

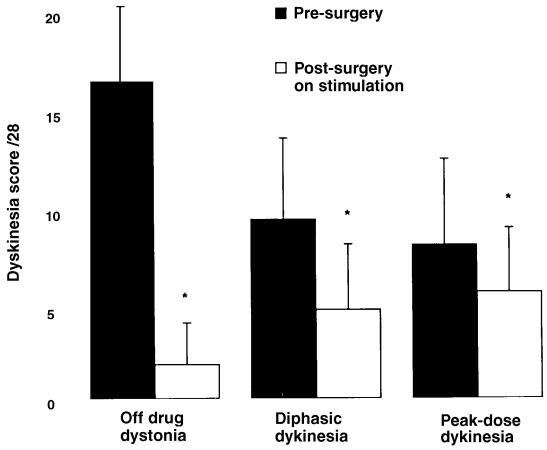

Fig. 2 Effects of chronic bilateral STN HFS, 6 months after surgery, on off-period dystonia, and on diphasic and peak-dose dyskinaesias in a levodopa test using the same dosage as before the operation. The chronic dopaminergic drug dose was reduced by 47% on average. The postoperative changes reflect both direct effects of STN stimulation and indirect effects related to drug modifications. $^{*}P < 0.05$.

Case report 1

Off-period dystonia

Preoperatively, the following dystonic features could be observed. Tonic frontalis contraction. A 90° torticollis to the left slowly evolving into left laterocollis, then into antecollis and finally right torticollis. Right shoulder abduction, elbow flexion and finger flexion. Left arm abduction and elevation above the shoulder, left elbow flexion. The right arm was passively brought into a normal position; after several minutes it very slowly returned to the above-mentioned position. Flexed trunk gradually evolving into marked lateral bending and then into 90° flexion. Left intermittent hip flexion, with the knee touching the trunk, and right knee flexion. Bilateral ankle flexion; the patient was able to walk with great difficulty on tiptoes. Intermittent supination and arching of the left foot. Extension and then flexion of the left big toe as well as flexion of toes II–V of the left foot. Foot dystonia improved with sensory stimuli, e.g. touching the dystonic foot or putting on slippers. Dyskinaesia score was 20/28. Off-period dystonia was accompanied by marked anxiety. Postoperative/on stimulation: no dystonia. Dyskinaesia score: 0/28. Postoperative after 12 h without stimulation: the preoperative dystonia recurred; 90° torticollis to the right, left arm abduction and elevation above the shoulder, left elbow flexion, hand extension and finger flexion, right foot flexion, left equinovarus foot and toe flexion. Dyskinaesia score 13/28. After switching on stimulation, the dystonia disappeared within a few seconds. When the stimulation was switched off, dystonia recurred within seconds but it took several minutes until the same dystonic posture was reached again. These findings were verified repeatedly at several follow-ups.

Diphasic dyskinaesias

Preoperative: fixed dystonia of the feet was replaced by repetitive movements beginning on the right side. There was a tremor increase in the left leg after 1 min, stereotyped repetitive movements started in the left hand after 2 min, there was a marked increase of tremor amplitude in the right arm and in parallel a disappearance of the left shoulder dystonia and a decrease in neck dystonia after 8 min.

Akathisia became evident after 9 min. Despite disabling repetitive movements of the lower limbs and hips, the patient tried to get up and walk around. Neck dystonia disappeared completely after 10 min. The patient walked with great difficulty due to dyskinaesias of the lower limbs. After 11 min there was typical choreodystonic posturing of the right hand while walking, indicating the transition to peak-dose dyskinaesias, and walking gradually improved. Dyskinaesia score 11/28. Postoperative/on stimulation: sudden onset of repetitive movements of the lower limbs predominant on the right together with choreodystonia of both hands and fingers and of the neck almost identical to postoperative peak-dose dyskinaesias. No ascending wave. Dyskinaesia score 6/28

Peak-dose dyskinaesias

Preoperative: conjugate upward eye deviation (with retrocollis) and lateral gaze deviation. Choreatic rapid neck movements in all directions. Choreodystonia of both hands. Lateral swaying of the trunk and copulation-like pelvic movements. Repetitive dystonic movements of the lower limbs, involving all the joints. Dyskinaesia score 15/28. Postoperative/on stimulation: conjugate eye deviation, choreatic neck movements. Mild choreodystonia of both hands. Repetitive dystonic movements of the lower limbs, involving all the joints predominantly on right. Dyskinaesia score 9/28

In the immediate postoperative phase, stimulation intensity was limited by choreodystonia of the upper limbs resembling the peak-dose dyskinaesias of this patient. Off-period dystonia was abolished and diphasic dyskinaesias were improved.

Case report 2

Off-period dystonia

Preoperative: painful lateral jaw deviation, inability to speak, mild antecollis, bilateral elbow flexion, right-hand extension, trunk flexion, 90° bilateral flexion of the hips, bilateral hip adduction, bilateral knee flexion, bilateral foot inversion, flexion of the toes alternating with toe extension. Dyskinaesia score 16/28. Off-period dystonia was accompanied by marked anxiety and respiratory distress. Postoperative/on-stimulation: dyskinaesia score 0/28.

Diphasic dyskinaesias

Preoperative: inability to speak with respiratory distress and an audible stridor (adductor dysphonia), repetitive flexion/extension movements starting in the right foot, then ascending to the knee and hip. Left dystonic hip flexion. Dyskinaesia score 10/28. Postoperative/on stimulation: dyskinaesia score 0/28

Peak-dose dyskinaesias

Preoperative: dystonic flexion/extension movements of the right fingers and hand. Minimal choreatic movements of neck, left arm, trunk and both legs. Dyskinaesia score 8/28. Postoperative/on stimulation: mild chorea of neck, left arm and right leg. Dyskinaesia score 4/28

In the immediate postoperative phase stimulation increase was limited by repetitive dystonic movements of the lower limbs exactly mimicking the diphasic levodopa-induced dyskinaesias of this patient

Case report 3

Off-period dystonia

Preoperative: Meige syndrome with prolonged blepharospasm. Painful neck dystonia varying from antecollis to left torticollis, retrocollis and finally right torticollis (Fig. 3). Bilateral elbow flexion. Flexion or extension of the fingers of the right hand, flexion of the fingers of the left hand. Left torsion of the trunk turning into hyperlordosis, then lateral bending to the right and finally marked flexion. Bilateral adduction of the big toe and flexion of toes II–V. Dyskinaesia score 20/28. Off-period dystonia was accompanied by marked anxiety. Postoperative/on stimulation: intermittent dystonic posture of the right foot on walking, repetitive right big toe extension during activation. Dyskinaesia score 1.5/28.

Diphasic dyskinaesias

Preoperative: dystonic neck rotation, bilateral repetitive elbow, hand and finger flexion/extension movements and finger abduction movements, lateral swaying of the trunk, bilateral dystonic flexion/extension movements of hips, knees, ankles and toes. Dyskinaesia score 12/28. Postoperative/on stimulation: blepharospasm, rotatory neck movements, bilateral extension of the proximal and extension of the distal phalanges predominantly on the right, internal rotation of the right leg, extension of the right knee, flexion and inversion of the right foot, extension and adduction of the right big toe, flexion of the right toes II–V, adduction of the left big toe. Dyskinaesia score 9/28.

Peak-dose dyskinaesias

Preoperative: mild generalized chorea sparing the face. Dyskinaesia score 6/28. Postoperative/on-stimulation: mild chorea of the neck and right leg. Dyskinaesia score 3/28.

In the immediate postoperative phase, acute HFS was able to induce repetitive flexion/extension movements in the upper limbs identical to the preoperative diphasic dyskinaesias. A further acute increase in stimulation intensity suppressed the diphasic pattern dyskinaesias and induced severe generalized chorea.

Summary of the semiological findings of LID

Off-period dystonia

Off-period dystonia typically appeared in the morning, worsening with exercise and loss of sleep benefit. Off-

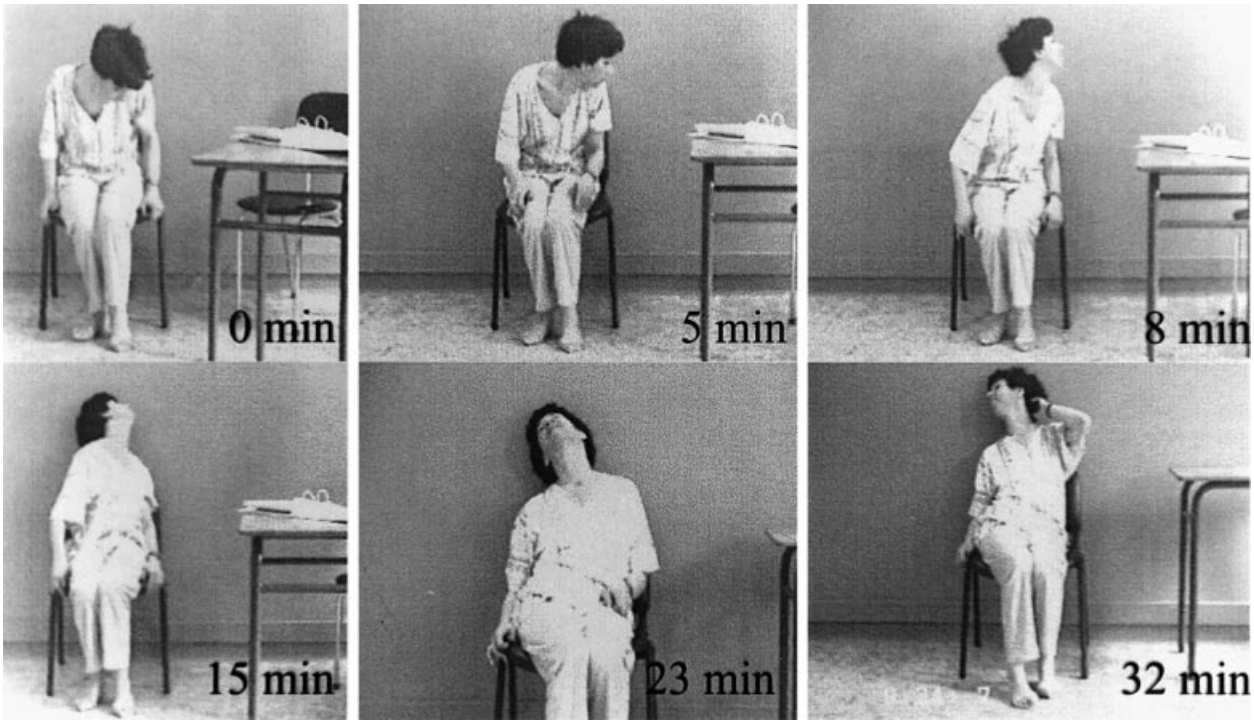

Fig. 3 Intra-individual variability of off-period dystonia within one body part, showing that off-period dystonia is not a single fixed dystonic posture but rather may represent slow movements. An antecollis posture slowly turns into left torticollis, then retrocollis and finally right torticollis (Case report 3), the whole sequence lasting 32 min. Pictures taken from a video recording. $*P < 0.05$.

period dystonia worsened during the neurological evaluation, including the UPDRS and timed tests. It most frequently affected the toes, causing flexion of toes II–V and extension of the big toe. The foot was frequently inverted and the ankle was either flexed or extended. In addition to this classical foot dystonia, however, other features of off-period dystonia were observed, most typically blepharospasm, neck dystonia, hand dystonia [the 'main creuse' of Garcin (Garcin, 1955)], truncal flexion and hip flexion, but all other body parts could be involved (e.g. jaw opening, laryngeal stridor, shoulder antepulsion, arm elevation, elbow flexion, abdominal dystonia, hip adduction, knee flexion or extension). Patients with off-period dystonia generally complained of pain in the muscles that were visibly involved in the dystonic postures. Pain or discomfort could also precede less visible dystonia, typically localized in the paravertebral region, most commonly neck and lower back pain or pain in the buttocks. In addition to pain, several patients suffered from a suffocating sensation and anxiety.

Off-period dystonia showed great variability over time; it waxed and waned over periods of minutes and could change from one body part to another. Beginning as a focal dystonia, it could spread into a segmental dystonia, hemidystonia or generalized dystonia. In one body part, dystonia could prevail in antagonistic muscles at different times. For example, an antecollis turned into a left torticollis, then a retrocollis and finally a right torticollis. The trunk was flexed and minutes later a lateral bending occurred. The foot was flexed and minutes later it was extended in a dystonic posture. Figure 3 illustrates the intra-individual variability of off-period dystonia. Although off-period dystonia was frequently provoked by exercise, e.g. dystonic claudication on walking, spontaneous fluctuations also occurred without any recognizable trigger factor. Off-period dystonia was improved with sensory tricks, by analogy with idiopathic dystonia. It could also be restricted to a specific motor task not involving another motor programme in the same limb. Off-period dystonia was most frequently seen on the side with the most severe parkinsonism, but the opposite occurred with on-period dyskinaesias, which were always the worst on the side most affected by parkinsonism. Off-period dystonia could change from one side of the body to the other, and occasionally prevailed on the side less affected by Parkinson's disease.

Diphasic dyskinaesias

Diphasic dyskinaesias could be the first symptom to indicate the action of levodopa or to herald the recurrence of parkinsonism after an on-period. In most patients, diphasic dyskinaesias disappeared completely during the peak-dose phase. In others, some of the diphasic features reappeared in between, depending on activation. End-of-dose dyskinaesias tended to last longer than the onset-of-dose dyskinaesias. Diphasic dyskinaesias also occurred together with or at the onset of dose, and could be preceded by other typical motor or non-motor symptoms that indicate levodopa response. These were yawning, the return of facial expression, dramatic

mood swings with the sudden disappearance of off-period depression, a sense of well-being and a return of initiative, often with transient logorrhoeic speech and akathisia. In one patient who was able to walk without freezing but with very slow shuffling steps in the off-period, diphasic akathisia was accompanied by marked freezing, which disappeared with the peak-dose effect of levodopa. A transient worsening of parkinsonism, such as difficulty in breathing or an increase in tremor, was gradually replaced by more irregular, slower repetitive movements. Effects ranging from transient anxiety to panic attacks could be observed. Transitory vegetative signs such as sweating, flushing, tachycardia and hypertension also occurred. At the onset of dosing, fixed dystonia disappeared in an ascending wave in the same way as parkinsonism. Fixed off-period dystonia often gradually changed into repetitive stereotyped diphasic dystonia in the transition from the off- to the on-period. Diphasic dyskinaesias could be activated by motor tasks, especially of the body part involved. They could be position- or action-dependent. Proximal diphasic limb dyskinaesias could be slow and dystonic or more rapid and ballistic. In addition to dystonia, myoclonus could be observed. Diphasic dyskinaesias were always more severe on the side most affected by Parkinson's disease.

Peak-dose dyskinaesias

There was minimal parkinsonism at the peak response and patients were not rigid but could be hypotonic. They lost some of the initiative seen during the onset of the dose phase and some became drowsy. Peak-dose dyskinaesias were mainly choreic in nature but also showed dystonic features, the movements being faster and less repetitive. The diphasic movements sometimes reappeared intermittently. Peak-dose dyskinaesias were activated by motor acts, even in distant parts of the body. Speaking, eating, the motor tests of the UPDRS and especially the timed tests markedly aggravated choreatic movements. Mental stress also worsened peak-dose dyskinaesias. They could be generalized, typically affecting the face, neck and upper limbs. Blepharospasm or facial grimacing was a frequent feature and ocular movements could also be involved. The neck often showed repetitive alternating rotation. The upper limbs showed a typical choreodystonic feature: the hand was flexed with a slight ulnar abduction, the fingers were flexed at the metacarpophalangeal joints and the distal joints were extended. The trunk showed dancing movements. The lower limbs also showed choreodystonic movements. Generalized chorea, even if embarrassing for the relatives, was mostly well tolerated by the patients, in contrast to off-period dystonia or diphasic dyskinaesias. It was not very disabling or painful and the patient was relieved from the parkinsonism, the psychiatric changes and distress of the off and diphasic periods. If the limbs were proximally affected, however, movements could be ballistic with functional disability. Peak-dose dyskinaesias were always more severe on the side most affected by Parkinson's disease.

Effect of STN HFS on dyskinaesias

When switching on the STN HFS postoperatively, the first sign to improve was off-period dystonia. Low HFS parameters had to be used in the immediate postoperative phase to avoid the induction of disabling dyskinaesias. During this period, HFS was less effective on akinesia than levodopa and could induce a diphasic pattern of dyskinaesias, which often mimicked the diphasic levodopa-induced dyskinaesias of the individual patient (e.g. Case report 3). An acute increase of either levodopa or HFS parameters suppressed both levodopa- and HFS-induced diphasic pattern dyskinaesias, sometimes then inducing generalized chorea or ballism (e.g. Case report 3). The stimulation-induced dyskinaesias gradually decreased with chronic HFS, allowing a gradual increase in stimulation parameters up to the optimal effect on akinesia. In parallel, the levodopa dose could be reduced. At the 6-month follow up, chronic STN HFS generally had almost the same effect on parkinsonism as levodopa at its best. The threshold for the induction of dyskinaesias either by HFS or by levodopa had increased. Off-period dystonia only rarely reappeared after overnight withdrawal of medication even if the stimulation was switched off overnight. If residual off-period dystonia recurred, then HFS with parameters effective on akinesia led to disappearance of the dystonia within seconds after switching on the contralateral STN stimulator. The duration of diphasic dyskinaesias was much shorter in the on-stimulation condition compared with the preoperative levodopa challenge, and there was an almost immediate transition from off-period akinesia to an on-period with peak-dose pattern dyskinaesias. STN HFS and levodopa showed additive effects on dyskinaesias: switching on the stimulation during a levodopa test shifted diphasic pattern dyskinaesias to peak-dose pattern dyskinaesias or worsened pre-existing peak-dose chorea. Even if dyskinaesias were reduced in intensity, the preoperative individual topographical and semiological patterns of off-period, diphasic or peak-dose dyskinaesias could still be recognized.

Discussion

The severity of off-period dystonia was reduced by 90% in the defined off condition at the 6-month follow-up on chronic STN HFS in comparison with the preoperative defined off condition. This was accompanied by a 66% decrease in pain during the off-period. During a levodopa challenge, using the same suprathreshold dose as before the operation and with the stimulation on, diphasic dyskinaesias were reduced by 50% and peak-dose dyskinaesias by 30%. The average daily levodopa equivalent dose was reduced by 47%. Therefore, on-period LID in everyday life were even more reduced than during the acute levodopa challenge using a high dose. Their duration decreased by 52% whereas their

intensity decreased by 68%. Severe, disabling off-period dystonia occurred in a third of our patients who had undergone surgery for severe dopa-sensitive parkinsonism with long-term motor complications, generally in patients with young-onset Parkinson's disease. Thus, it is not rare in surgical candidates and it may be the most disabling symptom that leads to an operation. There were no permanent side effects apart from a gain in weight, and all of the patients had major benefits from surgery with regard to motor function, pain and dyskinaesias. Patients with young-onset Parkinson's disease, characterized by severe akinesia, a high degree of sensitivity to levodopa and a tendency to develop severe dyskinaesias, especially painful dystonia, seem to be ideal candidates for bilateral STN HFS. Off-period dystonia tends to be more generalized than previously described. It appears in bouts, it may wax and wane with exertion or with loss of sleep benefit, and the muscles primarily involved may change within minutes from one part of the body to another, or from agonist to antagonist. This symptom is generally completely suppressed by STN HFS. STN HFS reduces diphasic dyskinaesias to a greater degree than peak-dose dyskinaesias. STN HFS is an interesting alternative to pallidal surgery for the treatment of levodopa-induced motor complications that cannot be sufficiently controlled by medical strategies.

Topographical distribution of off-period dystonia

Dystonia can occur in untreated parkinsonism (Charcot, 1892) and may be an early sign of the disease (Stewart, 1898), but chronic dopaminergic stimulation leads to a worsening of dystonia (Duvoisin *et al*., 1972) during the off-period, especially in the morning, several hours after the last intake of levodopa (Melamed, 1979). Off-period dystonia was most often more severe on the side more affected by parkinsonism, as described previously (Melamed, 1979; Ilson *et al*., 1984; Poewe *et al*., 1987). However, exceptions were found (Melamed, 1979; McHale *et al*., 1990; Marconi *et al*., 1994), and this relationship is less evident than that between diphasic or peak-dose dyskinaesias and the most affected side. In some patients dystonia was the first sign of the disease, preceding the onset of parkinsonism by several years, and it was located on the dominant side in these cases. Foot dystonia is typical in Parkinson's disease (Stewart, 1898; Melamed, 1979; Poewe *et al*., 1988). Approximately one-third of parkinsonian patients who receive treatment with levodopa for >5 years develop painful foot dystonia (Poewe and Lees, 1987). This study shows the distribution and variability of off-period dystonia in advanced Parkinson's disease in young, highly levodopa-sensitive patients. In this population, off-period dystonia is not restricted to the typical 'striatal toe' or inverted foot: all body parts may be affected. Off-period dystonia involving proximal parts of the legs or other parts of the body has been described only rarely (Ilson *et al*., 1984; Poewe *et al*., 1986; McHale *et al*., 1990). Generalized off-period dystonia is frequent in young-onset Parkinson's disease, by analogy with diphasic dyskinaesias (Lhermitte *et al*., 1977). Off-period dystonia is very distressing to the patient and it may occur with agonizing pain, difficulty in breathing (McHale *et al*., 1990) and marked anxiety. This often leads to a vicious circle, with increases in levodopa doses leading to a further worsening of the off-period dystonia. STN HFS is highly effective in suppressing this symptom.

Variability in time of off-period dystonia

Off-period dystonic postures are generally considered as fixed (Ilson *et al*., 1984), as opposed to the more mobile on-period or idiopathic dystonia. However, when observing patients over a period of time, it is evident that these postures vary slowly, over minutes. Off-period dystonia also shows intra-individual variability that is not seen in idiopathic dystonia and is more typical of dopa-responsive dystonia (Nygaard *et al*., 1991). For example, a patient may have an antecollis posture that very gradually evolves into laterocollis then into retrocollis. Early morning dystonia has been described to subside slowly after 1–2 h even if the first dose of levodopa is withheld (Marsden *et al*., 1982), but during a drug holiday it may reappear on several consecutive days before eventually disappearing completely (Melamed, 1979). Intermittent bouts of off-period dystonia have been described only rarely (Poewe *et al*., 1988), but are regularly observed during preoperative assessments and surgery, when patients go without dopaminergic therapy for many hours. Off-period dystonia waxes and wanes over time, typically worsening with physical exercise (Stewart, 1898) but often without any obvious contributing factor. Off-period dystonia disappears during sleep (Arnulf *et al*., 1998). The loss of sleep benefit and resulting changes in cerebral dopamine levels may play a major role in the pathophysiology of early morning dystonia. Bouts of dystonia seem to occur together with an increase in parkinsonism, but it is difficult to distinguish between immobility and increased tone due to painful fixed dystonia and an increase in akinesia and rigidity. Like idiopathic dystonia, off-period dystonia was sometimes modified by sensory tricks in our patients, and within one limb off-period dystonia was sometimes restricted to a particular motor programme, as in writing dystonia.

Is parkinsonian posture related to dystonia rather than to rigidity?

It was not possible to differentiate severe postural abnormalities due to akinesia and rigidity from axial dystonia in some of our patients. The typical flexed posture of a parkinsonian patient is generally thought to be due to rigidity. Denny-Brown (1962) discussed the relationship between parkinsonian rigidity and dystonia. According to his concept of 'flexion dystonia' in paralysis agitans, every stage of transition between plastic rigidity and dystonia can be found in extrapyramidal disease. A 'rigid dystonic' hand deformity,

which improved in a Parkinson's disease patient following anterior choroidal artery occlusion, led Cooper to investigate surgery for torsion dystonia (Cooper, 1958, 1977). Antecollis, adduction of the arms, flexed elbows, 'main creuse' (Garcin, 1955), flexed hips, flexed knees and flexed or extended ankles tend to be related to rigidity, but these features were commonly observed in the setting of severe generalized off-period dystonia in our patients. In contrast, inversion of the foot and flexion of the toes are considered to be dystonic postures, and foot dystonia has been described as the most prominent type of off-period dystonia (Poewe *et al*., 1988). If a posture is extended instead of flexed, e.g. extension of the big toe, finger, knee or elbow, or retrocollis, everybody will agree in calling this dystonia. This is even more obvious if there is a combination of flexion and extension, as is often seen in different combinations in the fingers or toes. We observed marked variability of dystonic postures during the off-period. In a selected population of young-onset severe Parkinson's disease patients with severe dystonia in one body part, we observed a tendency of the dystonia to generalize. These observations indicate that off-period dystonia may be more frequent and more generalized in severe Parkinson's disease than previously reported and that at least some of the features attributed to rigidity may be caused by dystonia. Moreover, off-period dystonia tends to evolve into stereotyped repetitive diphasic dystonic movements of the same limb, and finally into peak-dose choreodystonic movements associated with hypotonia. These movements, when dystonic, are not usually related to rigidity. When rating dystonia, it may be difficult to estimate the relative contributions of parkinsonism and dystonia to the resulting handicap during a task. Rating rigidity in a patient with a fixed dystonic posture is misleading.

Progressive transition from off-period dystonia to peak-dose dyskinaesias both with levodopa and STN HFS

A progressive transition from fixed dystonia in severely akinetic–rigid patients to mobile dystonia, chorea or ballism, with increasing benefit on parkinsonism, was observed both during the levodopa test and with STN HFS. During the levodopa test, generalized off-period dystonia disappeared in an ascending wave, similar to that described for the appearance of diphasic dyskinaesias (Marconi *et al*., 1994). Moreover, repetitive diphasic dystonic movements were often encountered in limbs which were in a fixed dystonic position during the off-period. In these patients, the repetitive diphasic movements could be interpreted as a repetitive waxing and waning of their off-period dystonia with an increasing rhythm. The appearance of peak-dose choreodystonic or choreatic dyskinaesias generally accompanies the disappearance of diphasic-pattern dyskinaesias and parkinsonism, muscle tone becoming minimal or even hypotonic. The same observations were made for dyskinaesias induced by STN HFS. Off-period dystonia is the first sign to disappear postoperatively with low-voltage HFS. Off-period dystonia disappears within seconds after switching on the contralateral STN stimulator using parameters effective against akinesia. Low-voltage STN HFS may induce diphasic pattern dyskinaesias which can mimic the diphasic dyskinaesias of an individual patient. A further increase in voltage then suppresses the diphasic pattern dyskinaesias and induces generalized choreodystonia. There seems to be a continuous spectrum from fixed dystonia in the off-period over a more intermittent diphasic dystonia to choreodystonia with decreasing STN activity, related either to increased dopaminergic activity or to higher STN HFS parameters.

Pathophysiological implications

In MPTP parkinsonism, a model of pure dopaminergic deficit, there is a glutamatergic neuronal hyperactivity of the STN (Bergman *et al*., 1994). STN lesions lead to a decrease in STN neuronal activity and subsequently to normalization of the parkinsonian triad in the MPTP model (Bergman *et al*., 1990) and in patients with Parkinson's disease (Gill and Heywood, 1997; Obeso *et al*., 1997). STN HFS has been shown to replicate not only the effects of an STN lesion on parkinsonism in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (Benazzouz *et al*., 1993) and on the parkinsonian triad in Parkinson's disease patients (Limousin *et al*., 1995; Krack *et al*., 1997*b*; Limousin *et al*., 1998), but, in the same way as a STN lesion (Martin, 1927), it can also induce dyskinaesias (Limousin *et al*., 1996). Although the exact mechanism of the effect of HFS is not known, these observations favour a functional inhibition of the STN. Based on the known pathophysiology of the STN, the results of the present study make it possible to speculate about the role of the STN in the pathophysiology of the different types of LID.

STN HFS mimics the action of levodopa: the UPDRS is improved to the same degree with either levodopa or STN HFS (Krack *et al*., 1998*b*; Limousin *et al*., 1998), both acting on the complete parkinsonian triad. The effects on dyskinaesias follow a similar pattern according to the level of dopaminergic activation or voltage. Off-period dystonia is abolished at a low level and diphasic pattern dyskinaesias occur at a higher level. At a further level, high dopaminergic activation suppresses diphasic dyskinaesias but may induce peak-dose dyskinaesias together with a maximal improvement in parkinsonism (de Saint Victor *et al*., 1992), an effect similar to that produced by acute high-voltage HFS. However, chronic dopaminergic activation or stimulation influences dyskinaesias in different ways. Whereas chronic levodopa therapy worsens dyskinaesias, chronic STN HFS tends to decrease dyskinaesias (Krack *et al*., 1997*a*) (Limousin *et al*., 1998). This difference might be related to the pulsatile activation of the dopaminergic system by levodopa, with subsequent pharmacodynamic changes superimposed on pharmacokinetic variations (Mouradian *et al*., 1989, 1990; Schuh and Bennett, 1993), whereas HFS is continuous. A similar progressive decrease in dyskinaesias is seen after

permanent lesions of the STN in non-parkinsonian patients (Shannon, 1990).

Off-period dystonia disappears within seconds after switching on the contralateral HFS and may recur within seconds following HFS arrest. Fixed dystonia can be a presenting symptom of Parkinson's disease (Stewart, 1898) and may thus be pathophysiologically close to Parkinson's disease. Off-period dystonia occurs only with parkinsonism and is directly improved by STN HFS together with the parkinsonian triad; thus, it is very likely to be associated with cellular hyperactivity in the STN. Off-period dystonia corresponds to a very low level of levodopa concentration, whereas total absence of levodopa after a drug holiday lasting a few days may lead to the disappearance of off-period dystonia (Melamed, 1979). The action of STN HFS on on-period dyskinaesias is more complex. Off-period dystonia may show a gradual transition to diphasic dyskinaesias with repetitive alternation of dystonic activity in antagonistic muscles (Marconi *et al*., 1994). It is likely that diphasic dystonia reflects an altered pattern of STN neuronal activity with alternating periods of hyperactivity (dystonia) and decreased activity (decrease in tone) in groups of cells responsible for a specific muscle. An increase either in dopaminergic stimulation or in the electrical parameters of STN HFS leads to a shift from the diphasic pattern dyskinaesias to peak-dose pattern dyskinaesias through a further decrease in cellular activity. Peak-dose dyskinaesias associated with maximal decrease in parkinsonism would correspond to STN hypoactivity induced by high-voltage HFS. This hypothesis fits well with dyskinaesias occurring after a spontaneous lesion of the STN in humans (Suarez *et al*., 1997) and with the schematic diagram of the basal ganglion pathophysiology in dyskinetic states (Albin *et al*., 1989). Levodopa and HFS have additive actions on parkinsonism and dyskinaesias, as both reduce STN activity.

The actions of chronic STN HFS on on-period dyskinaesias are threefold. First, there is a direct action reducing the hyperactive part of the altered pattern of STN activity and thus shifting diphasic pattern dyskinaesias to peak-dose pattern dyskinaesias. This may explain why the dystonic diphasic dyskinaesias are improved to a greater degree than peak-dose dyskinaesias. Secondly, the HFS induced improvement in parkinsonism allows a decrease in levodopa dosage, and thus a decrease in pulsatile dopaminergic stimulation, which is the basis of dyskinaesias (Mouradian *et al*., 1990; Bedard *et al*., 1992; Sage and Mark, 1992; Schuh and Bennett, 1993; Obeso *et al*., 1994; Blanchet *et al*., 1995; Syed *et al*., 1998; Colzi *et al*., 1998). Thirdly, by analogy with the progressive disappearance of dyskinaesias with time after a stable STN lesion (Shannon, 1990), there seem to be gradual pharmacodynamic changes in response to a stable change in STN neuronal activity related to the continuous mode of chronic STN HFS. In the immediate postoperative period, a setting of the electrical variables that is effective on parkinsonism induces dyskinaesias, and a gradual increase to optimal variables within days or weeks is necessary. Furthermore, the threshold of HFS-induced dyskinaesias increases with chronic HFS over time (Limousin *et al*., 1998).

The major output from the STN is to the GPi, which then projects mainly to the prefrontal cortex through the ventral thalamus. Dyskinesias are thought to be related to an altered pattern of GPi activity (Suarez *et al*., 1997) and not to a simple decrease in activity, because a lesion placed in the ventroposterolateral part of the GPi, supposed to be the sensorimotor part, abolishes all types of dyskinaesias. Pallidotomy dramatically reduces levodopa-induced diphasic and peak-dose dyskinaesias in Parkinson's disease (Lozano *et al*., 1995; Baron *et al*., 1996), tardive dyskinaesias (Wang *et al*., 1997) and idiopathic dystonia (Lozano *et al*., 1997; Ondo *et al*., 1998) as well as hemiballism consecutive to a vascular lesion (Suarez *et al*., 1997). In Parkinson's disease patients, dyskinaesias after apomorphine injections are associated with a decrease in the firing rate of GPi neurons (Hutchinson *et al*., 1997). The characteristics of pallidal neuronal activity in hemiballism were recently reported by Suarez *et al.* (1997). According to the figure shown in their paper, the average spike rate was much lower than that in Parkinson's disease patients even in the on-period. Long pauses in firing were interrupted by short high-frequency bursts. This is the type of pattern one would expect if the GPi were no longer driven by the STN. If off-period dystonia is related to overactivity of the STN, the GPi would also be overactive. So, a pallidotomy would improve off-period dystonia in the same way as it improves on-period dyskinaesias. STN HFS leads to a complete and dramatic arrest of off-period dystonia. The same has been observed in pallidal surgery. Given the major effects induced by STN HFS on various dystonic states, the involvement of the direct striatal–GPi pathway in the appearance of off-period dystonia may be minor.

Conclusion

Dyskinesias can be related either to hyper- or hypoactivity of the STN. A continuous spectrum of dopaminergic and STN glutamatergic activity is proposed as the basis of the continuous spectrum of the clinical symptoms (i) parkinsonism; (ii) off-period dystonia; (iii) diphasic dyskinaesias; (iv) hypotonia and peak-dose dyskinaesias. The pathophysiology of LID is not well understood, and the implication of different transmitters has been discussed (Bedard *et al*., 1992). Our findings indicate a key role in the glutamatergic STN–GPi interaction in the pathophysiology of not only parkinsonism but also dyskinaesias. The effects of levodopa seem to be largely mediated by this interaction.

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