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Involvement of the Medial Pallidum in Focal Myoclonic Dystonia: A Clinical and Neurophysiological Case Study

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Abstract: We successfully treated a patient with familial myoclonic dystonia (FMD), which primarily affected his neck muscles, with bilateral deep brain stimulation (DBS) to the medial pallidum, and investigated the role of the medial pallidum in FMD. A patient with FMD underwent bilateral implantation of DBS electrodes during which field potentials (FPs) in the medial pallidum and electromyograms (EMGs) from the affected neck muscles were recorded. The effects of high-frequency DBS to the medial pallidum on the FMD were also assessed by recording EMGs during and immediately after implantation, as well as 6 days and 8 weeks postoperatively. During spontaneous myoclonic episodes, increased FPs oscillating at 4 and 8 Hz were recorded from the medial pallidum; these correlated strongly with phasic EMG activity at the same frequencies in the contralateral affected muscles. The EMG activity was suppressed by stimulating the contralateral medial pallidum at 100 Hz during the operation and continuous bilateral DBS from an implanted stimulator abolished myoclonic activity even more effectively postoperatively. The phasic pallidal activity correlated with and led the myoclonic muscle activity, and the myoclonus was suppressed by bilateral pallidal DBS, suggesting that the medial pallidum was involved in the generation of the myoclonic activity. High-frequency DBS may suppress the myoclonus by desynchronising abnormal pallidal oscillations. This case study has significant clinical implications, because at present, there is no effective treatment for focal myoclonic dystonia. © 2002 Movement Disorder Society

Key words: medial pallidum; focal myoclonic dystonia; basal ganglia

Dystonia is a syndrome characterised by prolonged muscle contractions causing sustained twisting movements and abnormal postures of the affected body part(s).[1] Dystonia can be focal, affecting a single body part in isolation, or generalised, affecting two or more segments or the entire body. Primary dystonia is the most common form; primary suggesting that there is no structural abnormality in the CNS. Only relatively recently has primary dystonia been accepted as a neurological rather than a psychiatric disease. It is associated with abnormalities in the basal ganglia and is often hereditary.[2,3] Secondary dystonia describes a disorder in which dystonia develops after damage to the basal ganglia.[4,5]

Neurophysiological and functional imaging studies suggest that dystonia is caused by overactivity of the direct putamenopallidal pathway through the basal ganglia. This reduces inhibition by the medial globus pallidus of the thalamic input to the cortex or of motor centres in the upper brainstem;[6] hence, it leads to increased gain and lack of inhibitory control of motor mechanisms.[1] Intraoperative recordings suggest that, in primary dystonic patients, pallidal neurons have lower and more irregular firing patterns at rest than those found in normal primates.[7] Such a decrease in inhibitory GPi output is expected to lead to increased activity in thalamic target regions, but Zihr and colleagues[8] did not find this to be

A videotape accompanies this article.

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the case in recordings from the ventrolateral thalamus of patients with primary generalised dystonia. Instead, the ventrolateral thalamus of dystonics displayed increased bursting but reduced discharge rates overall. Nevertheless, this activity correlated with EMG activity in the affected muscles. One possible explanation is that the altered pattern of neuronal activity (timing, synchronisation, etc.) in basal ganglia nuclei may cause unstable oscillations in their output and these need not cause any overall change in average discharge rates.[9] If this is the case, then lesioning the pallidum might reduce the abnormal basal ganglia discharge and consequently correct oscillations in cortical and other motor areas.[10]

Familial myoclonic dystonia (FMD) is characterised by rapid, shock-like involuntary myoclonic muscle jerks with dystonic muscle activity. It is very rare; only 3% of all patients with idiopathic torsion dystonia seen over a 5-year period had FMD.[11] The pathophysiology of FMD is not clear. A few neurophysiological investigations suggest that the driving mechanisms of the myoclonic dystonia are subcortical in origin.[11] One report showed that FMD involving neck and limb muscles may be suppressed by epidural electrical stimulation at the cervical level.[12]

Because it is now known that the basal ganglia are involved in primary and secondary dystonia, we reasoned that abnormal medial globus pallidal activity might also help cause myoclonic dystonia. Therefore, we recorded pallidal field potentials during implantation of electrodes for chronic stimulation of the medial pallidum, together with surface EMGs of the affected muscles, and correlated the two. In addition, by recording EMG activity intra- and postoperatively when DBS to the medial globus pallidum was switched on and off, we were able to assess the efficacy of high-frequency electrical pallidal stimulation as a treatment for FMD.

PATIENT AND METHODS

Case Report

The patient was a 28-year-old man who had quick jerks of his head and sometimes the shoulders, often occurring after voluntary head or arm movements. Symptoms first appeared at the age of 15 years. His head turned continuously to the right (see Video, Segment 1), especially when he was under stress. Alcohol intake helped to relieve some of the symptoms. Motor examination revealed normal strength, muscular tone, and tendon reflexes, and no evidence of atrophy or fasciculation. During the episodes of dystonic contraction, the left sternocleidomastoid, the left trapezius, the right splenius, and the right trapezius were primarily involved. No muscle jerks occurred in his lower or trunk muscles. Sensory examination was normal.

Three of the patient's six uncles and his father had similar movement disorders affecting the head and sometimes the upper limbs. The diagnosis of FMD was made in 1993. The patient has sought treatment at various centres throughout the world and tried a large number of medications, including anticholinergic drugs, clonazepam, levodopa, and major and minor tranquilisers. None of these had any significant effect on his symptoms, nor had botulinum toxin injections into his left sternocleidomastoid, right cervical paraspinal, and right splenius muscles. He was assessed in the Radcliffe Infirmary, Oxford, for possible surgical treatment.

Given our previous success alleviating spasmodic torticollis with bilateral pallidal stimulation,[13] and the alleviation of primary dystonia that has been demonstrated after either DBS[14,15] or pallidotomy,[7,16] we offered this patient bilateral pallidal stimulation. There were no neurological, medical, or cognitive contraindications. In addition to the surgical procedure, intra- and postoperative neurophysiological recordings were made to obtain objective assessments of the effects of the surgery.

Electrode Implantation and Neurophysiological Recording

Disposable Ag/AgCl electrodes (59-8439; Harvard Apparatus, Kent, U.K.) were fixed with adhesive over the left sternocleidomastoid and right trapezius muscles for EMG recording. Guided by computed tomographic/magnetic resonance imaging (CT/MRI) -fused imaging (Radionics Image Fusion and Stereoplan), a macroelectrode was stereotaxically inserted in the right medial pallidum, as previously described.[17] The final location of the electrode was decided according to where stimulation at 100 Hz caused maximum suppression of movement-induced dystonic myoclonus. This location was assessed both clinically and by reduction of EMG activity.

A quadripolar electrode for chronic DBS (3387; Medtronics, U.K.) was then implanted in the selected target. The stimulating electrode had 4 × 1.5 mm contacts, each separated by 0.5 mm, so that the array covered 7.5 mm. The focal pallidal field potentials were then recorded between adjacent pairs of the four contacts and surface EMGs were simultaneously recorded at rest and during spontaneous and arm movement-induced myoclonus. The pair from which the largest field potentials were recorded that were related to the myoclonic activity was then stimulated at 100 Hz, pulse width of 210 μsec, gradually increasing the intensity up to 6 V, while EMGs were recorded and the patient was examined by a neurologist. Having established from these recordings that

the pallidal involvement was bilateral, it was believed that bilateral pallidal stimulation might be required. Therefore, a contralateral pallidal 3387 electrode was also implanted to the same target.

Having plated the electrodes to the skull, the patient was reanaesthetised and the stimulator lead was tunnelled to a Synergy pulse generator (Medtronics) implanted under his skin below his right clavicle. The stimulation parameters were then set on the basis of our intraoperative recordings.

EMGs were recorded 6 days and 8 weeks after the operation. The stimulator was switched off for a few minutes to assess the effects of DBS on the arm movement-induced myoclonus in the neck muscles.

Data Analysis

The neurophysiological data were digitised and displayed online on a PC screen, and every 60-second segment was saved on hard disk for offline analysis. The average length of the myoclonic episodes was approximately 10 seconds. Therefore, all the 60-second records were reviewed and 8-second segments, representing rest, movement-induced, and spontaneous myoclonus together with the effects of stimulation postoperatively were selected for further frequency analysis.

The recordings were first bandpass filtered (0.5–40 Hz) to cover the frequency range of dystonic myoclonus. Data were sampled at 250 Hz, continuously displayed on a screen, and saved on the hard disk every 120 seconds. The power at each frequency was then calculated by using a fast Fourier transform (FFT) and averaged over eight nonoverlapping windows, which gives a frequency resolution of 0.5 Hz in the power spectrum. To test for functional correlation between pallidal and EMG activity, the cross-spectral density (CSD), coherence estimates (Coh), and phase were calculated by using MATLAB (MathWorks, Natick, MA). Coherence is a statistical function used to estimate the probability that two independent signals are correlated at a given frequency, and it ranges from 0 to 1. A coherence of 0 indicates that the two signals are not linearly related, and a coherence of 1 means that the two signals are identical in frequency and in phase. These calculations were previously described by Lenz and associates[18] and recently by Hurtado an coworkers.[19] The coherence between two signals, A and B, is defined by:

$$Coh(A,B) = (CSD(A, B))^2/(Power(A) \times Power(B)),$$

where $CSD(A,B) = Power(B) \times conjugate\ of\ Power(A)$. To assess the significance level of the coherence function, the 95% confidence interval was calculated according to the expression described by Rosenberg and colleagues[20]:

$$95\%\ confidence = 1\text{-}(1\text{-}0.95)^{(1/(No.\ windows-1))}$$

taking the number of nonoverlapping windows into account. Phase was defined by the four quadrant arctangent of the real parts of the signals of A and B within $\pm \pi$. In addition to the coherence analysis, the averaged power spectra of EMG activity were compared on spontaneous versus movement-induced dystonic myoclonus and postoperative DBS on versus off.

Neuropsychological Assessment

This included psychometric assessments of nonverbal IQ, spatial skills, verbal fluency and confrontation naming, verbal and nonverbal memory/new learning ability, auditory and visual selective attention, executive function, and speed of information processing. He was also screened for any diagnoses on Axis I of DSM-IV and completed a semistructured preoperative interview.

RESULTS

Correlation of EMG Activity and Pallidal Field Potentials During Spontaneous Dystonic Myoclonus

No activity could be recorded in the right pallidum when the patient was at rest on the operating table (Fig. 1, left). Similarly, very little muscular activity (<10 μV in peak–peak amplitude) appeared on either EMG channels, except small ECG artefacts (~100 μV peak–peak amplitude). During a typical episode of spontaneous dystonic myoclonus, increased rhythmic activity appeared in both pallidal and EMG records on both sides. This activity gradually increased in frequency and amplitude over a period of 2–3 seconds to reach its peak and lasted for 6–8 seconds before it gradually ceased. Noticeably, the EMG trace of the left sternocleidomastoid was more complex and higher in amplitude than that of the right trapezius, which reflected the fact that the patient's spontaneous dystonic bursts were asymmetric, worse on the left side.

Offline analysis showed that the frequencies of the rhythmic activity in three pallidal channels were similar, approximately 4 Hz (Fig. 1, right), although there were differences in their peak power values. As we expected over the frequency range of 3 to10 Hz, the right pallidal FPs were highly correlated with the left EMGs with increasing phase values from −2 to 3.14 radians, suggesting that the pallidal activity lead the EMGs.

Dystonic myoclonus provoked by arm movements were associated with higher EMG amplitudes than the spontaneous episodes (Fig. 2), and the asymmetry in the amplitude of EMG activity between right- and left-side

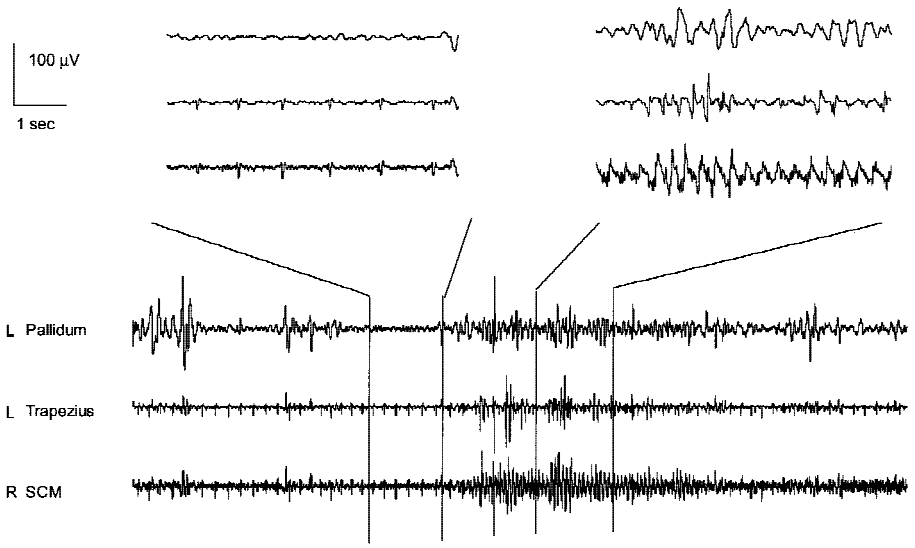

FIG. 1. Top: Selected 5-second recording segments to show the increased rhythmic activity in both pallidal field potentials (FPs) and surface electromyograms (EMGs) of neck muscles during myoclonic attacks (right) compared with resting condition (left). **Bottom:** Temporal correlation between pallidal and muscular activity during episodes of myoclonus was clearly displayed online over a period of 50 seconds. Recording sites are labelled to the right of the traces.

muscles was significantly reduced. However, the frequency of the EMG activity was similar.

Effects of Electrical Stimulation of the Medial Globus Pallidum on EMG Activity During Movement-Induced Dystonic Myoclonus

Once the intensity of pallidal stimulation was increased above 5 V, myoclonic EMG activity was suppressed (Fig. 3). Unilateral stimulation caused suppressions mainly of the contralateral but also the ipsilateral neck muscles. Figure 4 compares the power spectra of myoclonus provoked by arm movements before and during pallidal stimulation in left and right muscles; these revealed large amounts of EMG activity at around 4 Hz, with higher amplitude in the left sternocleidomastoid than the right trapezius muscle. The activity in both muscles in this frequency range was significantly suppressed by unilateral DBS.

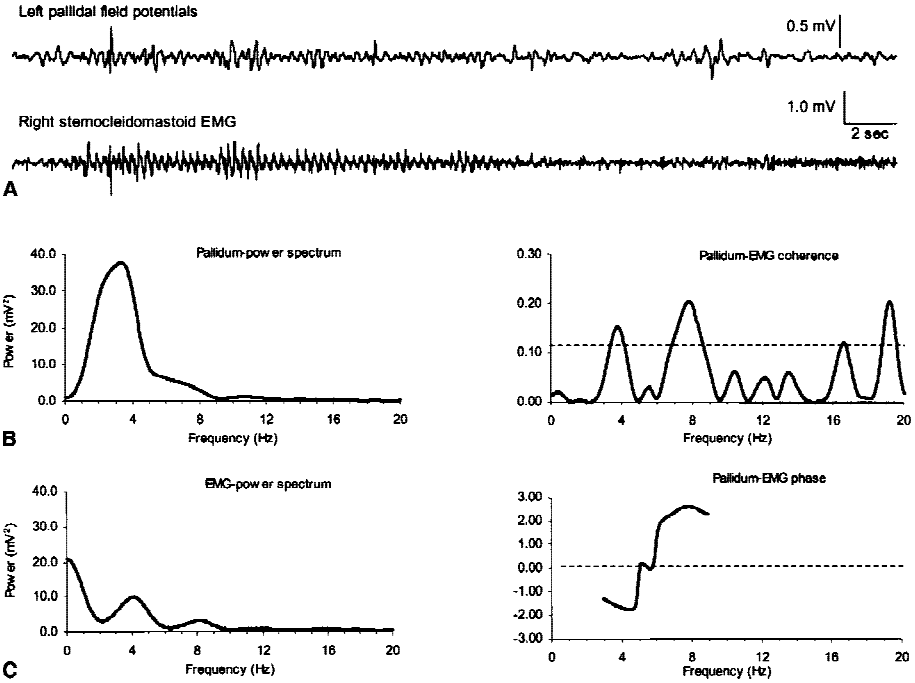

FIG. 2. Frequency analysis on pallidal field potentials (FPs) and electromyograms (EMGs) of 30 seconds (**A**) revealed a peak ranging 2 to 4 Hz in the pallidal potentials (**B,** left) and peaks at 4 and 8 Hz in the EMGs (**C,** left). Significant coherence estimates appeared at 4 and 8 Hz (B right, dotted line indicates the 95% confidence range) with up-going phase angles over the 3 to 9 Hz between two signals (bottom right, dotted line indicates phase angle zero), suggesting that the synchronised phasic neuronal activity in the pallidum functionally correlate with and lead to the rhythmic activity of the neck muscles.

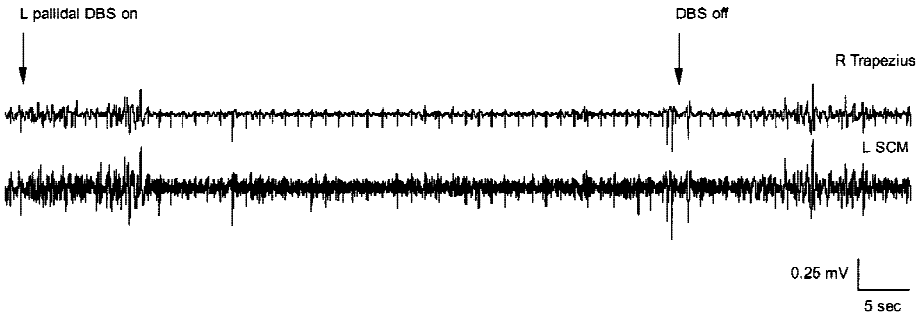

FIG. 3. During electrode implantation, the increased rhythmic activity in bilateral neck muscles was suppressed after test stimulation to the left pallidum and reappeared after the stimulation ceased. A delay of approximately 10 seconds existed between changes in stimulation and muscular activity. Stimulation on and off are indicated by arrows.

Postoperative EMG Recording With and Without DBS

Six days after implantation, we again recorded neck muscle EMGs during dystonic myoclonus induced by arm movements, first with no DBS and then when the DBS was on (130 Hz, 210 μsec pulse width, 6 V intensity). When the DBS was off, arm movements caused greatly increased muscular activity at 4 Hz. This finding was almost eliminated approximately 10 seconds after the stimulator was switched on.

Clinical and Neuropsychological Follow-up

After a further 8 weeks of continuous stimulation, EMG recording was repeated. Now, briefly turning the stimulation off did not cause the return of the myoclonic activity after arm movements (Fig. 5). The patient would not permit us to test the effects of longer periods with the stimulator off.

After 20 months of continuous bilateral pallidal stimulation (see Video, Segment 2), the persistent lateral and horizontal tilt of his neck has been abolished, and the spontaneous lightening jerks have been significantly suppressed. Myoclonus triggered by voluntary arm movements is significantly less frequent and reduced in magnitude. At neuropsychological assessment he denied any unintended postoperative sequelae; there was some persistent, mild anhedonia, but this was found to be associated with continued regret at the ending of a significant relationship. There was evidence to suggest that he was beginning to rebuild his confidence in public and reengage in social activities; he had also begun a new job. Comparison of baseline psychometric scores with scores obtained at follow-up revealed significant gains (ie, 1–2 S.D. units) on tests of story recall, spatial skills, and visual scanning/tracking; there was no deterioration in any domain.

DISCUSSION

In this patient with FMD primarily affecting the neck muscles, we carried out neurophysiological recordings of focal FPs and surface EMGs during and after stereotactic implantation of DBS electrodes to the medial pallidum. During spontaneous dystonic myoclonus, phasic activity of 4 and 8 Hz appeared in the globus pallidus. This activity was coherent with and led the rhythmic EMG activity in the contralateral sternocleidomastoid muscle.

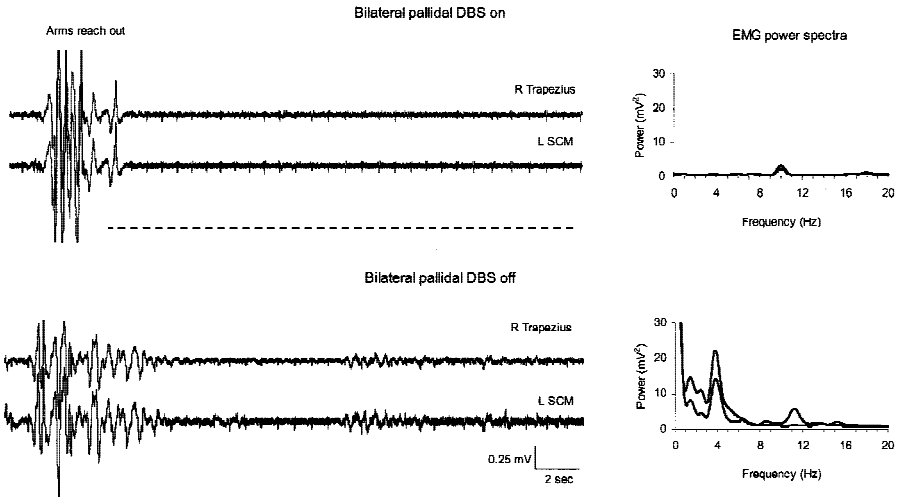

FIG. 4. Top: The stimulator was continuously on for 3 days after implantation. No rhythmic electromyograph (EMG) activity in the neck muscles was induced by voluntary reaching movements of the arm (left). In comparison (**bottom**), rhythmic EMG activity at 4 Hz was induced by the arm movements after the stimulator was turned off for a few minutes. Frequency analyses (right) were carried out over the data segments indicated by the dotted line.

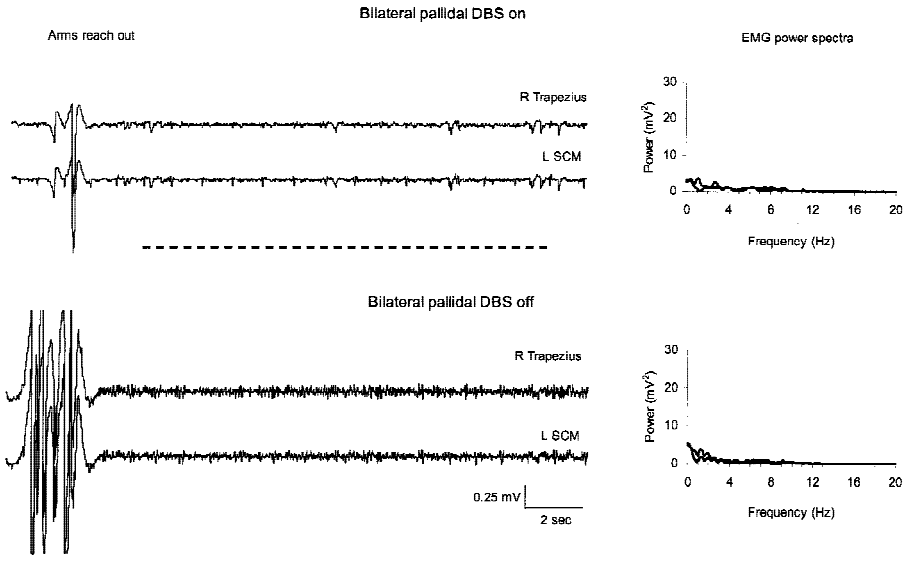

FIG. 5. After 8 weeks of continuous stimulation, the myoclonus induced by voluntary arm reaching was effectively suppressed even when the stimulator was turned off for a period of 20 minutes. Frequency analyses (right) were carried out over the data segments indicated by the dotted line.

The more severe myoclonus could be induced by voluntary arm movements and both spontaneous and movement-induced myoclonus were suppressed by high-frequency test stimulation during implantation. Continuous pallidal stimulation from an implanted stimulator eliminated the dystonia. After 8 weeks of chronic DBS, myoclonic activity did not return even during brief periods of switching off the stimulator.

The most interesting result was the functional correlation between the phasic FPs in the medial pallidus and the surface EMGs in the neck muscles during myoclonic episodes. Bipolar recording enabled us to detect 4 and 8 Hz oscillatory field potentials that were probably caused by abnormally synchronised activity of a large number of neurons in the medial globus pallidus. The patient (under local anaesthesia) was occasionally asked to briefly raise his arms to induce myoclonus in his neck muscles, during which no significant increase in pallidal activity was recorded nor did the muscular activity associated with voluntary arm movements significantly interfere with the DBS recordings, mainly because only the near field potentials generated locally could be detected by the adjacent pair of the DBS electrodes. Therefore, the significant coherence between the pallidal FPs and neck muscle EMGs suggests that the increased phasic activity in the globus pallidus was functionally correlated to the myoclonic activity in the muscles.

Vitek and associates[7] recorded single unit activity from the internal (GPi) and external globus pallidus (GPe) in patients with primary dystonia. They found that the normal regular firing of these neurons had been replaced by synchronous bursts of discharges. Moreover, individual neurons had developed greatly enlarged somaesthetic receptive fields. They proposed that the increased phasic activity could be accounted for by increased access of somatosensory afferents to the pallidum by means of the subthalamopallidal portion of the indirect pathway through the basal ganglia. Supporting this idea, Tempel and Perlmutter[21] found that in primary dystonia limb movements could induce abnormal cocontraction of muscles. Likewise, Zihr and coworkers[8] observed functional correlation between EMG activity in affected muscles and increased activity recorded from the thalamic target of the medial pallidum in patients with primary dystonia. As in our patient, arm movements could provoke, with a short delay, myoclonic contractions of the neck muscles, and as in patients with focal dystonia (writer's cramp),[22] dystonic postures or movements could be induced by the tonic vibration reflex manoeuvre. Thus, increased synchronised oscillatory activity in the pallidum may occur in both primary generalised and focal myoclonic dystonia.

Because we recorded the effects of high-frequency electrical stimulation in the medial pallidus on FMD at three different stages after the operation, we could observe relatively long-term changes. Whereas at operation, stimulation did not entirely abolish arm movement-induced myoclonus, after 6 days, continuous stimulation resulted in arm movements hardly inducing any myoclonus at all in the neck when the stimulator was switched on—but it returned immediately after switching it off. Interestingly, however, after 8 weeks of continuous DBS, suppression of dystonic myoclonus was not reversed when the DBS was briefly switched off.

The physiological basis of this beneficial effect of DBS on primary dystonia is unclear. Because spontane-

ous pallidal activity seems to be reduced in patients with primary dystonia,[7,23] reducing pallidal activity still further by lesioning or stimulating the pallidum or the pallidal thalamus should make dystonia worse. Instead, DBS may work by desynchronising the pathological bursting of pallidal neurons.[7] These may lead to involuntary muscle activity either by means of the thalamus and its ascending projection to the motor cortex or by means of the descending projections to the brainstem.[24,25] In our case of focal myoclonic dystonia, the highly synchronised pallidal FPs that led the muscular activity in phase were likely to have been the direct cause of the myoclonic attacks. Probably electrical stimulation desynchronised the excessive phasic activity in the pallidum so that its output ceased oscillating.

It was interesting that stimulation did not alleviate the myoclonic activity immediately but only after a delay of approximately 10 seconds. This delay is much longer than the conduction time from the pallidum to the muscles. Thus, desynchronisation can probably only take place after a large number of neurons have been recruited and their firing pattern gradually reset.

After 8 weeks of continuous DBS, unlike after a few days, suppression of myoclonus was not reversed when the stimulator was briefly switched off. Possible explanations include: (1) DBS in the pallidum likely interfered with the generator of myoclonus itself, rather than just blocking the conduction of activity along the motor circuit. In contrast, after switching off stimulation of the cervical cord, FMD returned immediately[12]; and (2) Prolonged stimulation must lead to the reorganisation of pallidal motor circuits over a lengthy time period. Thus, it is now clear that the alleviation of generalised dystonia that follows bilateral pallidotomy may take many months to complete.[26]

In this patient the FMD affected the left more than the right neck muscles during spontaneous episodes, but it was more symmetrical during movement-induced episodes. The enlarged receptive fields of pallidal neurons might mean that neurons would be more susceptible and perhaps more neurons would be recruited during voluntary arm movements than resting.

Legends to the Videotape

Segment 1: Preoperative video. The patient shows persistent mild lateral and horizontal tilt to the right in his head and neck associated with the spontaneous lightening jerks. The trunk and lower limbs are unaffected. Myoclonic jerks in his neck and shoulders are provoked by voluntary arm movements such as reaching.

Segment 2: Postoperative video. At 20 months follow-up of continuous bilateral pallidal stimulation, the lateral and horizontal tilt of his neck has been abolished and the spontaneous lightening jerks have been significantly suppressed. Myoclonus triggered by voluntary movements is less frequent with lower magnitude.

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