

## Short-Term Effect of Bilateral Subthalamic Stimulation for Advanced Parkinson's Disease

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**Background:** Subthalamic nucleus (STN) hyperactivity is a pathophysiological phenomenon of Parkinson's disease (PD). Inhibition of this hyperactivity by chronic deep brain stimulation (DBS) can possibly reset the aberrant function of the cortico-striato-thalamal circuit and improve the parkinsonian symptoms. DBS was introduced as a safe and alternative way of performing functional stereotaxic surgery for treating PD.

**Methods:** Seven advanced PD patients with complicated motor fluctuations and dyskinesia were enrolled in the study. A quadripolar electrode was bilaterally installed in the STN. Patients were evaluated before and 6 months after implantation using a battery of clinical assessments, including the motor score of the unified Parkinson's disease rating scale (UPDRS), modified Hoehn and Yahr (HY) staging, and the Schwab and England activities of daily living scale (SEADL). Preoperative baseline evaluations included both "off-medication" periods and "on-medication" periods, while postoperative evaluations included a cross-over of the above 2 periods with and without DBS.

**Results:** The motor disability, HY staging, and SEADL all significantly improved in both the off- and on-medication periods 6 months after STN DBS. Compared to the baseline off-medication score, a significant improvement was found in the UPDRS motor and other subscores including tremors, rigidity, and bradykinesia. The SEADL score showed a great improvement of 205.6%. Ballism/chorea, mood changes, and blepharospasm may have been induced by DBS. Neither serious nor permanent side effects appeared.

**Conclusions:** Bilateral STN DBS improved the motor symptoms in advanced PD patients in both the off- and on-medication periods. They showed improvements not only in motor disabilities of tremors, rigidity, bradykinesia, and postural and gait instability, but also in levodopa-related dyskinesia and psychosis.

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**Key words:** subthalamic nucleus, deep brain stimulation, Parkinson's disease.

Parkinson's disease (PD) is the most common neurodegenerative disorder resulting from loss of

dopamine neurons in the substantia nigra and a consequent deficiency of striatal dopamine.

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Cytoplasmic Lewy bodies found in the substantia nigra and locus ceruleus are the pathological hallmark of postmortem findings in PD patients. Dopamine replacement therapy by the precursor levodopa (L-dopa) with a dopamine decarboxylase inhibitor has been the gold standard treatment for PD since its advent during the late 1960s. However, L-dopa treatment is limited after 5-10 years by the development of a series of complications, including motor fluctuations, drug-induced dyskinesias, and psychoses. Due to the limitations of long-term L-dopa therapy, better knowledge of the pathophysiology of the basal ganglia through the modern technology of microelectrode recording and stereotactic neurosurgery has been pursued. The motor circuit model proposed by DeLong in 1990<sup>(1,2)</sup> further improved the fundamental understanding of the biochemical and pathophysiological bases of PD and its therapeutic approaches. According to the model, increased activity in the subthalamic nucleus is implicated in the motor abnormalities of PD and leads to an increased excitatory drive of the globus pallidum internum (Gpi) and substantia nigra reticulata (SNr). This in turn overinhibits the motor projections to the thalamus and reduces activation of the primary motor cortex, the premotor cortex, and the supplementary motor area (SMA). In experiments, inhibition of subthalamic nucleus (STN) activity by ablation or deep brain stimulation (DBS) in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated primates<sup>(3-7)</sup> or PD patients<sup>(8-13)</sup> has demonstrated a marked improvement in all dopa-responsive

parkinsonian signs. STN DBS was recently determined to be an effective and safe procedure<sup>(14)</sup> for advanced PD. We herein report on preliminary short-term results and side effects of 6-month STN stimulation on 7 patients with advanced PD. In addition, the synergistic effect of L-dopa and DBS in the induction of dyskinesia and dystonia is discussed.

## METHODS

### Patients

Seven advanced PD patients, including 1 female and 6 males, were enrolled in the study (Table 1). The mean age was  $57.3 \pm 8.8$  years, and the mean disease duration was  $12.1 \pm 2.8$  years. Five patients were unable to walk in Hoehn and Yahr stage 5 evaluated during an off-medication period. All subjects were clinically diagnosed as having probable idiopathic PD based on the criteria proposed by Gelb et al.<sup>(15)</sup> The subjects were selected on the basis of an initial good response to L-dopa fading, and the eventual development of severe motor fluctuations and severe off-period immobility. Exclusion criteria included significant cognitive dysfunction, other neurological or severe medical disorders, and severe brain atrophy as revealed by magnetic resonance imaging (MRI). One particular patient in our group had severe PD symptoms which could only be controlled with antiparkinsonian drugs. However, these drugs had the effect of inducing psychosis. This patient was given DBS as a last resort when other treatments had produced undesired complications.

**Table 1.** Clinical Characteristics of 7 Patients with Advanced Parkinson's Disease

Patient no.	Gender	Age (yr)	Onset age (yr)	Duration (yr)	H&Y*	LEDD <sup>†</sup> (mg)	UPDRS <sup>‡</sup> motor	Follow-up duration (mon)	Others
1	M	41	29	12	5	700	52	26	Dystonia, dyskinesia
2	F	54	36	18	5	200	96	24	Dystonia, psychosis
3	M	70	59	11	5	1100	51	16	-
4	M	59	50	9	2.5	1066	31	16	-
5	M	60	48	12	4	718	59	15	Dystonia
6	M	56	44	12	5	1400	93	13	Dystonia
7	M	61	50	11	5	1700	70	11	-

\*H&Y denotes Hoehn and Yahr stage (off-medication); <sup>†</sup>LEDD denotes the levodopa-equivalent daily dose. The following conversion factors were used: levodopa controlled-release preparations, 0.77; bromocriptine, 10; and pergolide, 100; <sup>‡</sup>UPDRS denotes the unified Parkinson's disease rating scale.

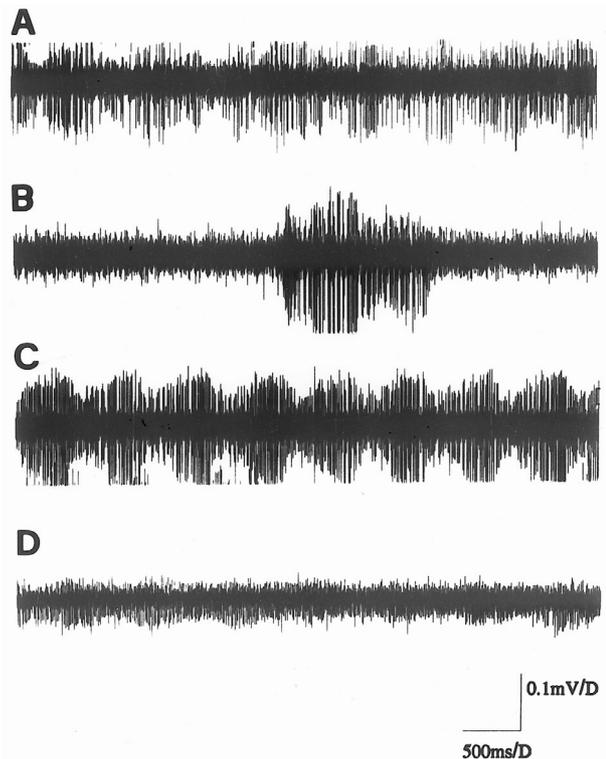
### Evaluations

Motor signs and disabilities were evaluated using the unified Parkinson's disease rating scale (UPDRS) motor score, Hoehn and Yahr (H&Y) staging, and Schwab and England score for activities of daily living (SEADL). The following variables of the UPDRS motor score were also calculated individually: tremors (mean items 20, 21), rigidity (mean item 22), bradykinesia (mean items 23-26), and posture and gait (mean items 28, 29). The levodopa-equivalent daily dose (LEDD)<sup>(16)</sup> indicating the levodopa dosage plus dopamine agonists was also determined. Patients were evaluated preoperatively in both off- and on-medication periods. Patients discontinued all antiparkinsonian medications 12 hours before any off-medication score was measured, whereas the on-medication score was obtained when the patient had his or her best response to the morning dose of antiparkinsonian medication. All postoperative evaluations, including the above assessments, were performed within a 2-day period 6 months after implantation, and included the following 4 conditions: off-medication without stimulation, off-medication with stimulation, on-medication without stimulation, and on-medication with stimulation. The percentage of change was defined as the difference between the preoperative baseline and the postoperative condition with DBS divided by the preoperative baseline.

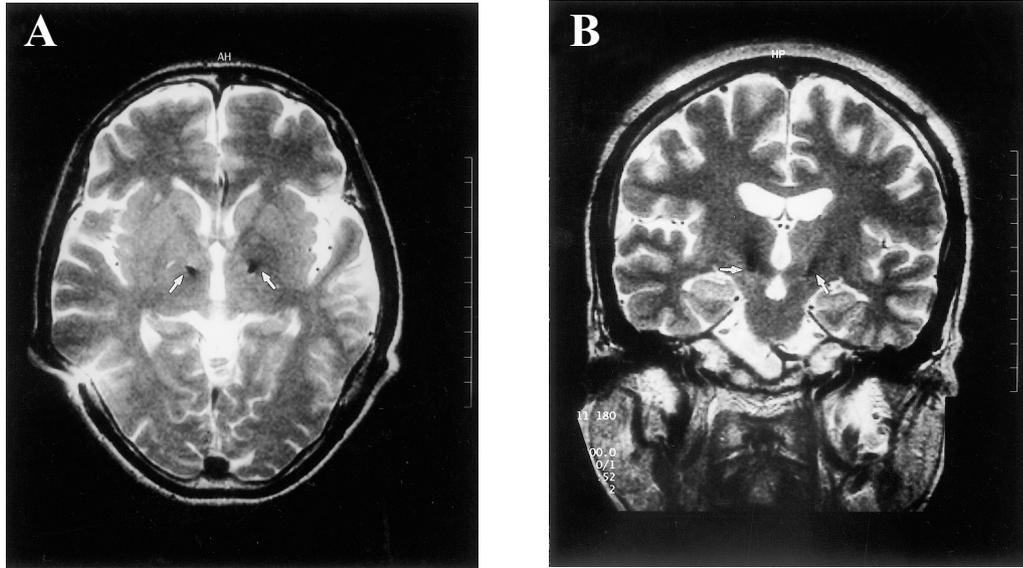
### Surgical procedures

Each patient discontinued all antiparkinsonian medications at least 12 hours before the surgical procedures. The subthalamic nucleus was first localized with a computed tomography (CT) scan and intraoperative microelectrode recording. A CT scan of the brain was done while a Brown-Robert-Wells stereotactic frame was fixed to the skull. Coordinates were initially chosen on a series of axial parallel slices to target the STN and were further matched to the computerized programs that contained a digital version of the Shaltenbrand-Wahren atlas. Thus the STN was located with a set of theoretical coordinates, commonly 12 mm lateral to the anterior commissural (AC)-posterior commissural (PC) line, and 2-4 mm below and behind the mid-intercommissural point in most of our patients. The microelectrode recording was begun just above the proposed target. Neuronal activities were recorded using a parylene-insulated

tungsten-tip microelectrode (0.3-0.5 Mohm impedance at 1000 Hz). The guiding cannula was the reference electrode. Extracellular action potentials were amplified with an amplifier (GS 3000, Axon Instruments) and simultaneously recorded using standard recording techniques (300-10,000 Hz), together with a descriptive voice channel. Spontaneous electrical activity was continuously recorded extracellularly along the trajectory. The neuronal activity of the STN was defined as having a high and irregular frequency (30-60 Hz), different to that of neighboring areas. The lower boundaries of the STN were a silent area followed by a higher frequency with a tonic pattern, indicating SNr. Neuronal activity responses to active or passive movement of the limbs or orofacial and tremor-related activity were considered to be the sensory-motor area (Fig. 1). A total STN span of 3-5 mm was expected and acceptable. Macrostimulation induced



**Fig. 1** Recordings along the microelectrode trajectory revealing different firing patterns of single unit activity in different neurons: subthalamic nucleus (A), motor-related neuronal activity (B), tremor cells (C), and substantia nigra pars reticulata (D).



**Fig. 2** T2-weighted MRI scans displaying the implanted permanent lead in the bilateral STN (arrows) on transverse (A) and coronal (B) sections.

paresthesia, contraction, or oculomotor response at low voltages, suggesting that the recording electrode might have been inadequately located. On the other hand, cessation of a tremor and provocation of dyskinesia were good signs. A permanent quadripolar electrode (3389, Medtronic) was then implanted bilaterally on the target, and contacts no. 1 and/or 2 were placed on the sensory-motor area. Stimulation was begun 2 weeks later after the edema effect in the STN had subsided. The contact positions of the permanent electrodes were reassessed and confirmed postoperatively by an MRI scan (Fig. 2).

#### Statistical analysis

The Wilcoxon signed-rank test (17) was used to test the change within patients.  $p < 0.05$  was considered statistically significant due to the small sample size, although multiple tests will inflate the probability of committing a type I error. When additional patients are available, a lower significance level will be considered.

## RESULTS

All 7 patients were regularly followed-up at least 6 months after the implantations were analyzed. The drug dosage for 2 of them was decreased by

50% after surgery, while 1 was totally free of antiparkinsonian drugs. The others were given a similar drug dosage to that of their preoperational conditions. Although the L-dopa dosage in 3 patients was reduced, it did not meet the statistical significance as established in our study.

When the off-medication and on-stimulation conditions were evaluated, the mean UPDRS motor score significantly improved by 53% compared with the baseline ( $p = 0.005$ , Table 2), which indicates that the major parkinsonian signs improved in the order of tremors, rigidity, bradykinesia, and posture and gait. Tremors in 5 patients were markedly reduced by 87.4%.

However, there were variations in the course of improvements. In 2 patients, tremors were immediately and completely reduced, similar to what occurs in patients receiving Vim stimulation.<sup>(16-18)</sup> In the remaining 3 patients, tremors were gradually suppressed over the following 6 months. Other features such as rigidity, bradykinesia, and posture and gait improved by about 50%. SEADL scores showed a dramatic 2-fold improvement. On stimulation, 5 patients in HY stage 5 were able to walk again independently, something which was impossible before. Off-period painful dystonia observed in 5 patients was also immediately relieved.

**Table 2.** Effects of Bilateral Subthalamic Nucleus Deep Brain Stimulation in 7 Patients with Advanced PD

Outcome measure	Score range	Mean score ( $\pm$ SD) off-medication				Percent change <sup>ⓧ</sup>	<i>p</i> **	Mean score ( $\pm$ SD) on-medication				Percent change <sup>ⓧ</sup>	<i>p</i> **
		Baseline pre-op	6 months DBS off	6 months DBS on				Baseline pre-op	6 months DBS off	6 months DBS on			
UPDRS motor*	0-108	65.7 $\pm$ 21.7	59.0 $\pm$ 23	32.8 $\pm$ 20.1	53%	0.005	39.0 $\pm$ 13.6	35.2 $\pm$ 22.4	19.1 $\pm$ 12.6	49.7%	0.040		
Tremors <sup>†</sup>	0-28	9.2 $\pm$ 4.8	6.1 $\pm$ 1.5	3.1 $\pm$ 0.6	87.4%	0.011	4.2 $\pm$ 1.6	3.14 $\pm$ 0.7	1.4 $\pm$ 0.5	61.0%	0.043		
Bradykinesia <sup>†</sup>	0-32	24.0 $\pm$ 7.6	22.0 $\pm$ 8.1	11.9 $\pm$ 7.6	49.0%	0.008	12.5 $\pm$ 4.7	17.6 $\pm$ 7.4	8.1 $\pm$ 4.2	29.0%	0.046		
Rigidity <sup>†</sup>	0-20	13.4 $\pm$ 5.4	13.6 $\pm$ 5.6	6.2 $\pm$ 5.9	55.9%	0.007	8.7 $\pm$ 4.2	6.7 $\pm$ 5.2	3.2 $\pm$ 2.9	53.7%	0.440		
Posture and gait <sup>†</sup>	0-8	5.6 $\pm$ 1.6	5.1 $\pm$ 1.8	2.9 $\pm$ 1.6	50.5%	0.005	3.3 $\pm$ 1.3	2.9 $\pm$ 1.7	1.4 $\pm$ 1.5	59.5%	0.440		
SEADL <sup>‡</sup>	0-100	22.9 $\pm$ 7.6	35.7 $\pm$ 21.5	70.0 $\pm$ 15.3	205.6%	0.005	70.0 $\pm$ 14.7	75.7 $\pm$ 17.1	85.0 $\pm$ 5.3	18.4%	0.005		
H&Y <sup>  </sup>	0-5	4.3 $\pm$ 0.3	3.5 $\pm$ 0.8	2.4 $\pm$ 0.7	43.9%	0.005	2.6 $\pm$ 0.5	2.6 $\pm$ 0.5	1.5 $\pm$ 1.0	45.2%	0.040		

\*: UPDRS total motor score (section III); †: Subcomponents of the UPDRS total motor score; ‡: The Schwab and England score for activities of daily living (SEADL) is based on a scale of from 0 to 100, with a higher score indicating a better function; ||: The Hoehn and Yahr stage of parkinsonism is based on a scale of from 0 to 5, with a lower stage indicating higher function; ⓧ: Percent change denotes improving percentage of the DBS on-condition compared with the preoperative baseline; \*\*: Significance of testing difference between pre-op and DBS on using the Wilcoxon signed rank test; DBS, deep brain stimulation.

In evaluating the on-medication and on-stimulation conditions, the mean UPDRS motor score also showed a modest but significant improvement of 19.1% ( $p=0.04$ ) (Table 2). All parkinsonian disabilities improved except rigidity and posture and gait. Three patients readily developed stimulation-related ballism/chorea; 1 of them had previous levodopa-induced dyskinesia. It was possible to resolve this stimulation-induced ballism/chorea by adjusting the location or the voltage of the stimulation. Interestingly, it seemed that a synergistic effect of L-dopa and STN stimulation contributed to the induction of dyskinesia. These dyskinesias had gradually subsided by 3 months later. Blepharospasms were induced in 5 patients when using a higher stimulating voltage (> 3.5 V). Transient confusion and agitation shortly after surgery were also noted in 3 patients. The complications gradually subsided over 1 to 2 weeks. Two patients developed hypomania with the presence of talkativeness, compulsive shopping, and mirthful laughter. The symptoms were reversible by adjusting the stimulation parameters.

All patients gained weight. Night sleep also improved in all patients due to the enhanced mobility during sleep.

## DISCUSSION

We have demonstrated that bilateral STN DBS has an outstanding short-term effect on parkinsonian

disabilities, particularly in the off-medication period in a preliminary study on a small consecutive series of 7 Taiwanese patients with advanced PD. These results are similar to those of previous reports.<sup>(8-10)</sup> The greatest improvement among parkinsonian disabilities was that for tremors followed by rigidity, bradykinesia, and axial symptoms in the off-medication period. Tremors showing the best response is also similar to most reports, except for a small group of patients described by Moro et al.<sup>(18)</sup> Most of the parkinsonian symptoms were significantly reduced shortly after stimulation was initiated. The improvement in tremors, however, took a variable course: some patients showed an immediate response, while others took longer to improve. It seems that the improvement in tremors by STN DBS differed from that induced by thalamic Vim stimulation.<sup>(19-21)</sup> A further study of the mechanisms underlying these different styles of tremor improvement will be undertaken. The most substantial benefit of STN DBS was the improvement in the activities of daily living, which can help advanced PD patients achieve a satisfactory and almost independent life again.

A significant effect on parkinsonian symptoms was also revealed in the on-medication period, although this additional effect was modest. It indicates a synergistic effect of L-dopa and stimulation. Certainly, we would expect this synergistic effect to more easily induce dyskinesia and/or dystonia in advanced PD patients. The same phenomenon has

been well described previously in many reported patients who were prone to develop dyskinesia when dopamine agonists were added to the L-dopa. The synergistic effect of L-dopa and STN DBS has never been reported in a posteroventral medial pallidotomy<sup>(16)</sup> or fetal nigral transplantation.<sup>(22)</sup> The improvements in rigidity and posture and gait did not reach statistical significance in the on-medication period with stimulation conditions. This was probably due to personal variabilities and the small sample size. The LEDD had not significantly decreased in 4 patients 6 months after surgery. This could have been due to the limited sample size and follow-up duration. The 1-year follow-up evaluation revealed that LEDD was reduced by at least 50% in all patients (unpublished data).

The key factor in the improvement of all parkinsonian disabilities by STN DBS was suppression of STN overactivity, which has been well investigated in MPTP-induced monkeys and PD patients. However, the mechanism by which stimulation decreases STN overactivity remains unknown.

The fact that even the maximum benefit of DBS was dramatic but no better than the best effect of L-dopa, and that patients with different features responded differently to the stimulation, indicates that suppression of STN overactivity is not enough to combat all PD motor problems. Perhaps the motor circuit model is still too simple to cover all PD motor disabilities.

A special patient (Table 1, patient 2) with severe psychosis was also enrolled in the study due to the fact that the effects of the drug had decreased to such an extent that the patient's daily routine was being adversely affected by parkinsonian symptoms. Both the parkinsonian features and the psychotic symptoms had gradually improved 6 months after surgery. Several questions regarding hallucinations in PD remain controversial or unanswered. Recently, a large study of the prevalence and risk factors of hallucinations in PD suggested that hallucinations affect 1/4 of PD patients. Moreover, the duration of PD, and not the age at onset was an independent predictor of hallucinations in a multivariate analysis.<sup>(23)</sup> Determining whether or not PD patients should undergo STN DBS requires further investigation.

The development of stimulation-induced dyskinesia (ballism/chorea) in 3 patients is quite interesting. This phenomenon has previously been described

in several patients.<sup>(24,25)</sup> It possibly indicates that the subthalamic nucleus is profoundly suppressed like the dyskinesia induced by an apomorphine injection or subthalamic nucleotomy. Similarly, the dyskinesia was more easily induced in our patients by the stimulation while on medication, the so-called synergistic effect. This caused problems in the early postoperative adjustment period. However, we found that these involuntary movements gradually diminished after chronic STN stimulation. The dyskinesia in 1 of 3 patients was improved by reducing the L-dopa dosage, as other reports have described.<sup>(24,25)</sup> In cases where the dose of L-dopa was constant, the anti-dyskinesia effect might have been caused by involvement of the pallidofugal pathway, which mimics a pallidotomy, in turn prohibiting the ongoing hemibalism.<sup>(2,26)</sup> The constant high-frequency stimulation might also prevent or reverse the downstream change induced by pulsatile stimulation of the dopamine receptor. Meanwhile, disruptions of the pathologic stimulation in turn stabilized the network of basal ganglia with respect to motor application. However, the mechanism of the relationship between STN and dyskinesia is still controversial.<sup>(25,26)</sup>

We conclude that bilateral STN DBS might be a safe and effective surgical procedure, which offered satisfactory improvement in our 7 patients with advanced PD. No significant complications were found except for mild emotional changes in 2 patients. Determining the mechanism of improvement by STN DBS and the long-term effects requires further investigations with a larger sample size.

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## 雙側視丘下核刺激治療嚴重型帕金森氏病之短期術後成效

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**背景：**視丘下核的過度活化被認為是帕金森氏病的基本病理機轉。用深部腦刺激術來抑制該核之過度活性。可能可以調整腦皮質~紋狀體~視丘迴路之功能進而改善帕金森氏病的症狀。

**方法：**本研究包含7名嚴重的帕金森氏病人。皆有運動起伏或亂動症等併發症。將一永久性之刺激電極植入病人二側大腦視丘下核，並以長久刺激。一系列的臨床評估在術前及術後6個月依有藥效，及有無刺激等情況分別實施。所得之分數以統計、分析。

**結果：**在有藥效及無藥效的狀況下，視丘下核深部腦刺激皆明顯改善病人之活動。在無藥效期之比較，深部腦刺激在術後6個月的UPDRS運動評估項目改善達53%，其他顫抖，僵硬，行動緩慢，步態及姿勢穩定Hoehn與Yahr病期等皆有改善，Schwab與England生活指數改善達205.6%類似改善亦見於有藥效期。在深部腦刺激下有部分病人產生暫時性的舞蹈症、情緒變化及眼痙攣症等，此外並未發現嚴重或永久之併發症。

**結論：**雙側視丘下核深部腦刺激有效改善帕金森病人於有藥效期及無藥效期之動作症狀，其中不只改善顫抖、僵硬、動作緩慢及步態穩定更包括因藥劑量減少而改善之亂動情形及精神症狀。

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**關鍵字：**視丘下核，深部腦刺激，帕金森病。

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