

## Surgical treatment of Parkinson's Disease

The surgical treatment of movement disorders is over a century old but went into a steep decline in the 1970's with the introduction of effective drug therapies such as levo-dopa. However, about a decade ago Laitinen reported on the success of pallidotomy for the treatment of advanced Parkinson's disease, which led to a resurgence of interest in functional neurosurgery for movement disorders. This coupled to an increased understanding of the underlying neural mechanisms and circuitry involved in basal ganglia disorders with improved surgical techniques and the development of deep brain stimulation (DBS) technology has paved the way for major advances in the treatment of Parkinson's Disease (PD).

### HISTORICAL BACKGROUND

Surgery for PD has passed through several phases during its evolution, of which three major stages can be identified - (1) Non-basal ganglia procedures, (2) Open basal ganglia procedures and (3) Stereotactic basal ganglia procedures.

The recognition that in some cases of stroke, contralateral loss of tremor occurred, prompted Horsley in 1909 to perform excision of the motor cortex in a case of athetosis with good effect. However, at least two decades passed before this work was extended to patients with PD by surgeons such as Bucy (1939). Tremor was reduced with some hemiparesis but the technique was not adopted widely as identification of the motor strip was difficult, rigidity and akinesia remained and post-operative epilepsy was a common problem.

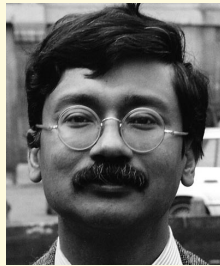
At around this time other procedures which were explored including cervical dorsal rhizotomy, cord section, cerebellar dentatectomy and bilateral corticospinal tractotomies but all were later discarded because of their ineffectiveness.

In the 1940s and 1950s Meyers focused attention on the basal ganglia and reported a 60% improvement in rigidity and tremor following the combined section of pallido-fugal fibres, resection of the caudate head and anterior capsulotomy. Subsequently an anecdotal observation by Cooper (1953) led to a new approach. In a case of attempted pedunculotomy for parkinsonism, the procedure had to be abandoned because of bleeding which was controlled by clipping the anterior choroidal artery. The patient not only survived, but had good amelioration of symptoms and no deficit despite infarction of the globus pallidus. Procedures such as these led the way for modern stereotactic neurosurgery.

By the early 1950s a small area of the basal ganglia was defined as the optimal target in surgery for Parkinsonism, comprising the medial pallidum and the ansa lenticularis. The tools capable of reaching these targets without causing damage along the approach were available in concept from the late 19th century and are described by Harting of Utrecht (1861) who designed the "kephalograph" to make directed intracranial lesions in the experimental animal and Zernov (1889) who developed the "encephalometer", successfully used to treat superficial brain lesions.

The breakthrough in the development of human stereotactic surgery came in 1947 when Spiegel and Wycis, who by extending the original frame designed by Horsley and Clarke (1908), introduced the stereo-encephalotome, which used landmarks within the brain, rather than the skull. Parkinsonism could now be treated by thermal lesion or injection of alcohol (chemo-pallidectomy) in the thalamus, ansa lenticularis and pallidum.

### Authors



**Professor Aziz** studied physiology at University College London graduating in 1978. During this time he developed his keen interest in the role of the basal ganglia in movement disorders. He studied medicine at King's College London (1978-1983) and obtained his surgical fellowship in 1987 following which he has pursued a career in neurosurgery. He is currently a consultant neurosurgeon at the Radcliffe Infirmary, Oxford and Charing Cross Hospital, London. He is an expert in functional neurosurgery and has a special interest in the surgical treatment of movement disorders including dystonia.



**Mr. John Yianni** trained at University College London, qualifying in 1996. He completed his basic surgical training in Oxford, obtaining his surgical membership in 1999. Subsequently he joined the Oxford Movement Disorder Group based at The Radcliffe Infirmary Oxford, where he is currently clinical research fellow working towards an MD. His field of interest includes stereotactic functional neurosurgery for movement disorders, in particular dystonia.

Lesions in the thalamus more reliably abolished tremor, so that by the late 1950s this had become the preferred target, particularly the ventrointermediate (Vim) nucleus.

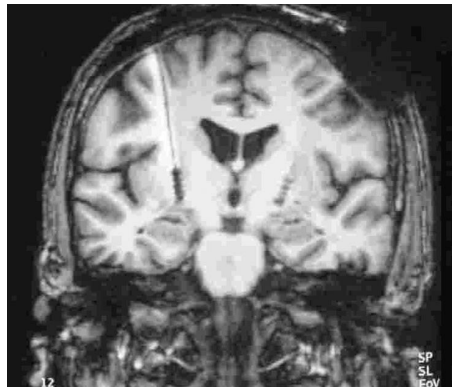
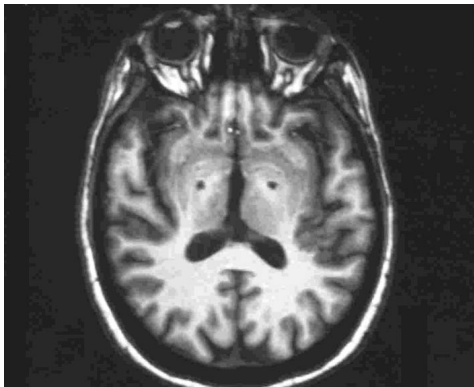
Interest in stereotactic surgery for Parkinson's disease all but disappeared following the introduction of levodopa in 1968. However, the increasing numbers of PD patients with dyskinesias and motor fluctuations that ensued prompted pursuit of a surgical solution. Interest in Pallidotomy was renewed in the 1980s, and by the mid 1990s its effectiveness had been confirmed by many groups, particularly in the alleviation of levodopa induced dyskinesias. Unpredictable results with the transplantation of foetal dopamine cells and adrenal medullary grafts into the striatum, furthered the cause in favour of lesional surgery but concern remained regarding high complication rates, particularly following bilateral procedures.

### DEEP BRAIN STIMULATION (DBS)

By the 1960s, the use of intraoperative stimulation of brain targets in preparation for ablative surgery had established the concept that high frequency Vim stimulation suppressed tremor. This technique was initially used to identify the optimal site for thalamic lesioning. However by the late 1970s and early 1980s, therapeutic rather than diagnostic uses of DBS for PD were occurring. High frequency electrical DBS is thought to work by providing an adjustable inhibitory effect on the target site. It has the advantages over lesional surgery of being reversible, adaptable and avoids concern about the adverse cognitive and bulbar effects observed following bilateral lesions. Though effective, DBS requires careful postoperative adjustment, averaging 40 hours of adjustment for optimum benefit and maintenance of effect in certain patient groups. The replacement of equipment when hardware failure occurs (wires moving, breaking or becoming infected) is a further consideration with estimates in the region of 20%. The stimulation battery unit also requires replacement every three to five years depending on target and parameter settings. Occasionally this entails emergency admission following dramatic rebound symptoms that have been observed following acute stimulator failure. DBS therefore necessitates considerable long-term commitment from the team looking after the patient. Consequently there remains a place for "palliative" thalamotomy or pallidotomy in certain situations.

Although results following DBS can be impressive, they are dependent on careful patient selection. With the exception of tremor, successful surgical treatment of Parkinsonian symptoms is reliant upon the presence of a dopaminergic responsive system. "Burned out" cases, with no useful "on" periods, will not respond to surgery. Similarly non-dopa responsive parkinsonian diseases, such as multiple system atrophy, will not significantly benefit from surgery. It is crucial that patients with significant cognitive or psychiatric difficulties are avoided.

Drug induced hallucinations, postural instability and dysphonia, particularly in the "on" state are further poor prognostic signs. Although the temptation is to offer surgery because little else can be done, it must be considered that surgery carries with it at least a 3% risk of significant morbidity or mortality resulting from intracerebral haemorrhage. This makes the trade off between possible risks and potential benefit not sufficiently favourable to recommend surgery in these patients.



**Lesional Surgery.** Post-operative axial MRI scan of patient following bilateral pallidotomy for PD.

**DBS.** Coronal MRI scan of a patient following implantation of bilateral electrodes into the GPI.

## TARGETS FOR DBS IN TREATMENT OF PARKINSON'S DISEASE

### Thalamus

Historically, chronic thalamic stimulation had already been used for the treatment of chronic pain. However because the thalamus is the final common outflow pathway for all tremors, contralateral tremor is reliably suppressed with DBS in the region of Vim. The majority of studies that have evaluated thalamic stimulation have reported approximately 90% improvement in tremor of the contralateral limb, whilst avoiding the adverse effects on speech and cognitive function related to thalamotomy. Although tremor is markedly improved in PD, there is sometimes no significant improvement in activities of daily living as there is no effect on bradykinesia and although dyskinesia is occasionally helped, this is not a reliable observation. Even patients with tremor predominant Parkinson's disease will normally develop bradykinesia in time, so it is now recommended that such patients should have STN rather than thalamic stimulation, reserving thalamic surgery for non-Parkinson's disease tremor.

### Pallidum

Based on the success of DBS for tremor and of pallidotomy for parkinsonian symptoms, Siegfried and Lippitz (1994) used the technology of DBS for continuous stimulation of the posteroventral globus pallidus internus (GPI). Posteroventral pallidal stimulation will reliably abolish contralateral dyskinesias. This includes biphasic and peak dose dyskinesia, and "off" state dystonias. The improvement in "off" state bradykinesia also occurs, as does contralateral tremor but this is not a reliable effect. Medication remains unaltered following the procedure. Axial symptoms, including dyskinesias, non-dopaminergic gait and bulbar function do not improve, whilst "on" state postural instability and freezing may be worsened. Other potential side effects include visual field defects (optic tract), hemiparesis and dysarthria (internal capsule). Weight gain is also frequently observed, probably resulting from reduction in dyskinesias as well as functional improvements that may aid feeding.

### Subthalamus

Bilateral subthalamic stimulation alleviates all the principal symptoms of tremor, rigidity and bradykinesia. In 1993 Benebid reported stimulation of the subthalamic nucleus (STN), which improved almost all parkinsonian symptoms allowing substantial reduction of dopaminergic medication. Drug induced dyskinesias are also reduced, although unlike pallidal surgery, this occurs by

the resultant reduction of medication postoperatively. On stimulation or lesioning of the pallidum or STN, transient dyskinesias may ensue, which are usually a predictor of successful outcome. Unilateral surgery can be offered to patients with very asymmetric disease, but most require bilateral surgery to avoid problems with variable medication requirements on the two sides. Adverse effects are very frequent during electrical stimulation of the subthalamic area and include dystonic symptoms, paraesthesia and oculomotor effects. There is also concern about the frequency of psychiatric side effects, particularly depression that probably arises as a result of the inhibition of STN limbic areas. As this can occur in the absence of any previous history of mental disorder, patients with a history of significant depression should not be offered STN surgery, since the observed rate of suicide has been high in some series.

## SUMMARY

In summary, there is no doubt that there remains a definite role for neurosurgical intervention in the treatment of PD. Particularly with reference to DBS, dramatic benefits with a relatively small risk of adverse effects, are achievable in experienced hands. Robust comparative trials are however urgently required, not only to validate the effectiveness of DBS but also to help determine the cost effectiveness of this relatively expensive treatment. Confirming the mechanisms by which these systems exert their effect also carries considerable importance as this could potentially provide new insights for the development of future neuroprotective therapies.

## Further Reading

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