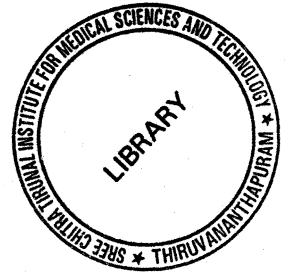
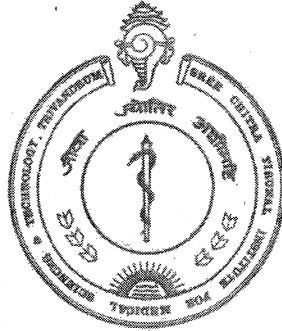


Subthalamic Nucleus Deep Brain Stimulation : Outcome Of Various Methods For Targeting And Accuracy Of Electrode Placement



Submitted for MCh Neurosurgery

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September 2010

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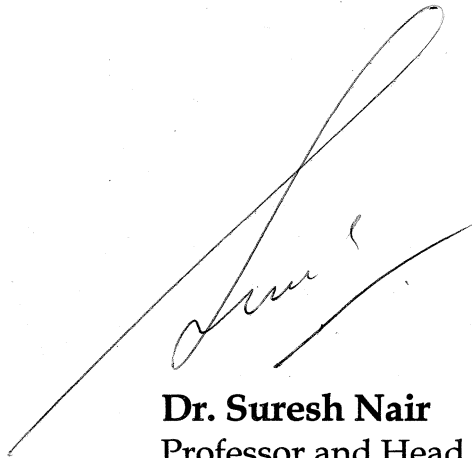
Submitted by : Dr. Amit Sadashiv Dhakoji

Programme : MCh Neurosurgery

Month & Year of submission : September 2010

CERTIFICATE

This is to certify that the thesis entitled " Subthalamic Nucleus Deep Brain Stimulation : Outcome Of Various Methods For Targeting And Accuracy Of Electrode Placement " is a bonafide work of Dr. Amit Dhakoji and was conducted in the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram under my guidance and supervision.



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DECLARATION

This thesis titled “Subthalamic Nucleus Deep Brain Stimulation : Outcome Of Various Methods For Targeting And Accuracy Of Electrode Placement” is a consolidated report based on a bonafide study done by me during October 2006 to July 2009 under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

This thesis is submitted to SCTIMST in partial fulfillment of rules and regulations of MCh Neurosurgery examination.



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ACKNOWLEDGEMENT

The greatest force, the **Almighty God** is all powerful. He was with me always guiding and showing me the path of wisdom.

The guidance of **Dr. Suresh Nair**, Professor and Head of the Department of Neurosurgery, has been invaluable and I am extremely grateful and indebted for his contributions and suggestions, which were a valuable help during the entire work. He will always be a constant source of inspiration to me.

I owe a deep sense of gratitude to **Dr. Ravi Mohan Rao** for his invaluable advice, encouragement & guidance, without which this work would not have been possible.

The critical remarks and suggestions of **Dr. Girish Menon**, helped me in achieving a high standard of work.

I am deeply indebted to **Dr. Krishnakumar**, who helped me immensely throughout my thesis and always gave me valuable suggestions and critical remarks.

I would also like to thank **Dr. Mathew Abraham, Dr. Easwer H V, Dr. Gopalakrishnan C.V, Dr. George Vilanilam , Dr. Vikas, Dr. Jayanand** for their constant encouragement & support.

I also wish to thank **Dr. Asha Kishore** , Movement disorder specialist as well as **Mr. Gangadhar Sharma** for extending their constant support, and valuable help throughout my thesis period.

Last but not the least , I owe a deep sense of gratitude to all my patients without whom this work would not have reached this stage.

Dr. Amit Dhakoji

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INTRODUCTION

INTRODUCTION

Deep brain stimulation (DBS) involves the placing of electrodes deep inside the brain to deliver electrical current to target nuclei. It has been in clinical practice since 1989¹ and to date has been used to treat millions of patients worldwide². The most common conditions treated are advanced Parkinson's disease, tremor, dystonia and chronic pain, chronic depression, obsessive compulsive disorders and epilepsy. Parkinson's disease [PD] patients represent the largest cohort of those treated with DBS. In this group, DBS has been shown to be safe and cost-effective, conferring up to 70% clinical improvement at 5 years and significantly improving quality of life in comparison to other treatments³. In preliminary primate studies, DBS of the subthalamic nucleus has also been shown to potentially reduce the rate of disease progression, a feature not seen with other treatments^{4,5}. Various methods have been used for targeting STN, including Schaltenbrand-Wahren atlases, indirect formulae based on measurement from AC-PC line and recently direct MR visualisation of STN. With the advent of neuronavigation, precise localisation and calculation of safe trajectory has become possible.

By its nature, the success of DBS is directly dependent on the accuracy by which the target structures deep inside the brain are reached. An electrode which is slightly off target is unlikely to confer the maximal potential benefit

and also likely to be associated with undesirable side effects as neighbouring structures are 'stimulated' by current spread and stimulation parameters are increased in order to achieve a clinical benefit. Furthermore, verification of the position of the implanted electrodes is required postoperatively to interpret clinical results and to enhance our understanding of basal ganglia physiology.

High-resolution stereotactic neuro-imaging protocols are therefore of crucial importance. Magnetic resonance imaging (MRI) offers superior visualisation of the DBS target structures relative to computed tomography (CT), but previous adverse incidents have heightened concerns about the risks of postoperative MRI with electrodes in situ ^{6,7}. As a result, many neurological centres are moving toward using CT for postoperative imaging in place of MRI. But while CT offers excellent positional accuracy and clear delineation of the electrodes, it lacks the soft tissue contrast necessary for visualisation of the target structures. An alternative technique to verify electrode tip position is to register and fuse the preoperative nonstereotactic MRI with preoperative stereotactic CT on the day of surgery. The preoperative nonstereotactic MRI offers better anatomical definition of the nuclei, the patient is on medication and without frame, thereby increasing the comfort levels, the images can be loaded on the workstation a few days prior to the surgery to allow detailed planning to be done and saving precious time on the day of surgery when a quick stereotactic CT is performed and fused on the workstation to obtain stereotactic coordinates of the target nucleus. A nonstereotactic postoperative

CT is obtained, which avoids the aforementioned safety issues. A further advantage of postoperative CT is that it provides a clearer delineation of the electrode tip relative to that provided by postoperative MRI, as the signal change on CT is associated with metallic X-ray attenuation rather than signal void and distortion artefact from MRI ⁸ . Therefore, the fused postoperative CT/preoperative MRI may encompass the benefits of both modalities, offering an alternative method for evaluating electrode position relative to the target structures, without the need for postoperative MRI.

REVIEW OF LITERATURE

EVOLUTION OF MOVEMENT DISORDERS SURGERY

Surgery of the basal ganglia circuitry for treatment of movement disorders was not performed until Meyers, in 1939, pioneered his innovative techniques⁹. Meyers performed such techniques as transventricular section of pallidothalamic pathways, extirpation of the head of the caudate nucleus and the globus pallidus pars interna (GPi). Parkinsonian symptoms improved in about 60% of patients; however, these procedures were burdened with high morbidity and a mortality rate of 12%¹⁰.

The next step in the development of functional neurosurgery for movement disorders included electrocoagulation of the pallidofugal pathways via subfrontal or transsylvian approaches¹¹.

The introduction of stereotactic neurosurgery revolutionized the surgical treatment of movement disorders. The first stereotactic frame was constructed in 1908 by the neurosurgeon Horsley and the mathematician Clarke for use in animal studies to investigate cerebellar physiology. It was not until 1947, however, that this technique was applied to humans. Spiegel and Wycis performed dorsomedial thalamotomies and pallidotomies with the goal to modify afferent stimuli and emotional reactions in patients with choreic and athetotic syndromes^{12,13}. Subsequently, the method also was used in PD

patients by neurosurgeons and neuroscientists worldwide. The first ventrolateral thalamotomy for treatment of parkinsonian motor symptoms was performed in 1952 by Mundinger in Freiburg, Germany, in collaboration with Hassler and Riechert ¹⁴.

Erroneously, the development of stereotactic pallidotomy and thalamotomy have been attributed to Cooper. In 1952, Cooper accidentally severed the anterior choroidal artery during pedunculotomy for parkinsonian tremor. Postoperative improvement of the tremor, however, which was thought to be related to pallidal infarction, led him to the use of anterior choroidal artery ligation and only later to pallidotomy. Likewise, when Cooper reported the unexpected striking improvement when a planned pallidal lesion was misdirected to the thalamus in the late 1950s, thalamotomies had already been done in many other centers.

In the early period of functional stereotactic surgery, lesions were created using leucotomes, injection of alcohol and procaine oil, inflation of balloons, ultrasound, implantation of radioactive pellets, cryosurgery, and electrocoagulation. Later, all these techniques were almost completely replaced by radiofrequency lesioning. In the early 1960s and mid-1960s, most surgeons abandoned pallidotomy in favor of thalamotomy for the treatment of movement disorders. The subthalamic region was approached via lesions directed to the zona incerta ¹⁵.

The number of functional stereotactic operations, however, dropped rapidly after the introduction of levodopa in clinical routine. Subsequently, in the late 1970s and 1980s only a few centers continued to perform thalamotomies, particularly for treatment of tremor and hyperkinetic movement disorders.

The interest in surgical therapy arose again when the limitations of levodopa therapy became apparent in PD, in particular the gradual loss of efficacy with development of motor fluctuations and dyskinesias. The revival of neurosurgery for movement disorders started in the mid-1980s when Laitinen et al. reintroduced Leksell's posteroventral pallidotomy and showed that this procedure almost eradicated levodopa-induced dyskinesias .¹⁶

Increased attention was focussed on surgery for PD when the first results on autologous transplantation of adrenal medullary tissue to the striatum were reported in 1987. The rediscovery of pallidotomy by Laitinen had a major impact on the further development of functional stereotactic surgery for movement disorders¹⁶. This sparked a never-before-seen interest among neurosurgeons and movement disorder neurologists alike in surgical treatment , especially after interpretation of microrecording in normal monkeys and 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys provided a rational basis for pallidotomy¹⁷.

The introduction of ventralis intermedius nucleus (VIM) deep-brain stimulation (DBS) for tremor by the Grenoble Group went largely unnoticed at first, but with the expansion of applications and targets, especially the subthalamic nucleus (STN), pallidotomy as a procedure became obsolete and DBS for movement disorders became the cornerstone of surgery for movement disorders.

The importance in human stereotaxy of collaborative teamwork between clinicians of affiliated specialties, especially nonsurgical, for the analysis of clinical symptoms, decision-making, and evaluation of results cannot be overemphasized ¹⁸ .

There have been two milestones in the introduction of DBS for movement disorders. The first, the introduction of thalamic stimulation for tremor, was based on clinical research and empirical surgery, in the absence of animal models for tremor or basic research on the mechanisms of DBS ¹⁹. The second, the extension of this technique to the STN ²⁰ and the globus pallidus pars interna (GPi) ²¹ for all parkinsonian motor symptoms, was driven mainly by progress in basal ganglia pathophysiology ²² . But another important contribution was the empirical discovery of the dramatic effect of pallidotomy on levodopa-induced dyskinesia , not predicted by the new basal ganglia model but compatible with earlier findings of subthalamic dyskinesias in the animal model ²³.

Over the next few years, multiple reports described the beneficial effects of pallidotomy on the clinical triad of parkinsonism and on levodopa-induced dyskinesia, which confirmed efficacy on contralateral symptoms ^{24,25,26,27}. Because of common side effects associated with bilateral pallidotomies, however, physicians continued to search for alternative therapies. The subthalamic nucleus STN seemed to be a promising target, but as lesions of the STN were known for their potential to induce ballism, it seemed that the STN could not be explored with ablative surgery. DBS had been effective in improving different tremors when applied to the VIM, with DBS mimicking the effects of a lesion. It was, therefore, tempting also to apply this reversible technique to other targets, such as the STN or the GPi. The mechanism of action, however, remained unknown, and thus efficacy in one target could not simply be referred to another target. Benazzouz et al. finally found the missing link when they showed that DBS stimulation in the MPTP monkey could replicate the antiparkinsonian effects of an STN lesion ²⁸. With awareness of these results, the Grenoble Group successfully applied STN DBS in PD patients.

Based on the reports of efficacy in the MPTP model, which is a levodopa-sensitive model of PD, patients who were highly levodopa sensitive were selected. Because of the risk of inducing dyskinesia, these first patients were selected to have both relatively little dyskinesia and, as the surgery was experimental, an advanced stage of the disease. In these patients, a first

unilateral STN stimulation was administered, although improving contralateral symptoms, it did not improve any severe functional handicap related to axial symptoms, such as gait disturbance. However the antiakinetic effect was spectacular after the first patient had been operated on bilaterally in this new target ^{20,29} . As expected, STN stimulation-induced dyskinesias ³⁰ ensued, and this side effect slowed the initial enthusiasm. However, it could be shown that reduction of levodopa was possible and that dyskinesia gradually improved with chronic STN stimulation ³¹. STN stimulation also was shown to have a marked effect on parkinsonian tremor. DBS also was applied to the internal pallidum, replicating the antiparkinsonian and antidyskinetic effects of a pallidal lesion, with the relative safety of the technique allowing for bilateral surgery ²¹. Based on its first experience with bilateral pallidal and subthalamic stimulation, the Grenoble Group started to prefer STN stimulation over GPi stimulation because its better antiakinetic effect allowed for marked reduction of levodopa ³² .

The antiparkinsonian effect of STN stimulation showed a good correlation with the antiparkinsonian effect of levodopa, and thus levodopa sensitivity has become a major selection criterion for STN surgery ³². The long-term effects of STN DBS in PD are well established now . Although today most centers performing DBS prefer the STN DBS to the GPi DBS in PD patients, this issue concerning the relative advantages and disadvantages of both targets is not settled yet ³³.

From the beginning of human stereotactic surgery, intraoperative stimulation has been a key technique for evaluating accurate electrode placement, mainly using the unwanted physiologic effects of stimulation as evidence of the electrode being out of target. It has been known from the beginning of human intraoperative electrophysiology. That electrical stimulation could inhibit parkinsonian tremor in the same site where rhythmic activity synchronous to tremor was recorded and where thalamotomy would also suppress tremor, and this knowledge was used to define the target ³⁴. Albe-Fessard, who had introduced microrecording and first described a tremorogenic rhythm in the thalamus, discussed the mechanisms of this tremor inhibition using stimulation ³⁵.

In the 1990s, based on advancements in the understanding of the pathophysiology of basal ganglia ¹⁷, the surgical target of interest moved to the STN and GPi. Reports of improvement in the primate MPTP model of parkinsonism after lesions in the subthalamic nucleus²² were published around the same time that Laitinen et al. published the results of a series of pallidotomies in patients with PD who showed improvement in akinesia, rigidity, and tremor. In fact, Laitinen had taken up as a target the posteroventrolateral part of the pallidum, which already had been successfully operated on in the sixties by Leksell before the advent of levodopa.

PRINCIPLES OF MOVEMENT DISORDERS SURGERY

FUNCTIONAL ANATOMY AND TARGETS

A major principle of basal ganglia organization is that striatal projections are segregated into discrete pools on the basis of their projection targets. Striatal output to the GPi involves both a direct pathway that is GABAergic and an indirect pathway via the globus pallidus pars externa (GPe) and the STN. The STN is thought to play a pivotal role by regulating the output of the GPi. Although this simplified model has been criticized often, it explains at least partially the effect of basal ganglia surgery. The GPi has an inhibitory GABAergic projection to the ventrolateral (VL) thalamic nucleus, which is also referred to as the motor thalamus. Until recently, Hassler's nomenclature subdividing the VL into the nucleus ventralis anterior (Voa) and nucleus ventralis posterior (Vop) was the terminology most commonly used^{36,37}. The nucleus ventralis intermedius (Vim) is located just posteriorly to the Vop. The pallidofugal fibers reach the thalamus via the ansa and the fasciculus lenticularis and are directed to the Voa, while the Vim receives afferents from dentatothalamic pathway.

SOMATOTROPIC ORGANISATION OF SUBTHALAMIC NUCLEUS

The subthalamic area is composed of the zona incerta, the STN, and white matter containing the fields of Forel. The STN is connected to the GPe and the GPi via pathways that traverse the internal capsule. The zona incerta is the ventral extension of the nucleus reticularis thalami.

Some investigators have found that most of the neurons in patients with PD responsive to passive manipulation or active movements of the limbs were in the lateral portion of the GPi with the upper limb and the axial body presented more frequently further lateral and in the ventral one-third, and the lower limb in the dorsal one-third. There is no clear somatotopy in the vertical axis for the distribution of tremor-related cells. Microelectrode recording studies in the STN have shown that all neurons with sensorimotor responses were in the dorsolateral region of the STN with arm-related neurons lateral to leg-related neurons, and presentation of the oromandibular musculature in the middle of the sensorimotor region, ventral to the arm and leg ³⁸.

STEREOTAXIS AND ATLASES

The principles of stereotactic surgery include the acquisition of data from various imaging modalities and their transfer to a Cartesian coordinate system ³⁹. In functional stereotactic surgery, these coordinates are generally referenced to the stereotactic frame that is rigidly fixed to the patient's head. Stereotaxis has been derived from the Greek, meaning three-dimensional arrangement. The Cartesian coordinate system implies that any point in space can be determined by 3 coordinates (x, y, and z), which are defined with regard to 3 intersecting orthogonal planes. These 3 planes the abscissa, ordina, and applicata intersect at 1 point that is commonly defined as 0 (zero). By convention, the x coordinate defines the distance to the midsagittal plane (right to left), the y coordinate defines the distance to a reference point along the

rostrocaudal axis (anterior to posterior), and the z coordinate defines the distance to a reference point in the coronal plain (superior to inferior). Because stereotactic positive-contrast ventriculography was the method of choice in functional stereotactic neurosurgery long before the advent of contemporary imaging methods, it generally has been accepted that it refers the coordinates of a target in the basal ganglia or in the thalamus to anatomic landmarks in the third ventricle. Commonly, the interconnecting line between the anterior commissure (AC) and the posterior commissure (PC), the intercommissural line, is used for this purpose. The general acceptance of the AC and PC as landmarks has resulted in the generation of stereotactic atlases, such as the Schaltenbrand-Bailey atlas and its newer edition, the Schaltenbrand-Wahren atlas ⁴⁰. These atlases contain series of myelin-stained brain sections 1-4 mm thick in each of the 3 orthogonal planes. The atlas coordinates should be corrected in patients with shorter or longer intercommissural lines or widening of the third ventricle. Because these coordinates do not account for individual spatial variability, intraoperative physiologic confirmation and refinement of the target are necessary ⁴¹.

PRINCIPLES OF STIMULATION: MECHANISM OF DEEP-BRAIN STIMULATION

There is still no consensus on the physiologic mechanism underlying the effects of DBS. The comparable effect of stimulation to ablation in the thalamus on tremor, and in the STN and internal segment of the globus pallidus

(GPi) on the motor signs of PD, have led many investigators to conclude that DBS acts to suppress neuronal activity, decreasing output from the stimulated site. Therefore, the starting hypothesis was that high-frequency electrical stimulation is neuroinhibitive⁴². It seems that DBS can activate fibers locally, which would deliver high-frequency synchronous bursts feeding the projection targets with either favorable gamma activity or a disrupted message.

In patients, frequency of stimulation is the crucial parameter, since no beneficial effect can be obtained below 50 Hz, and a plateau is reached with frequencies of 100-200 Hz^{19,20}. A depolarization block is possible, but the effective frequency of stimulation seems too low to induce such an effect, and the possibility for its maintenance in the long term is questionable, whereas the clinical effects of DBS seem permanent.

In the STN, stimulation at a frequency greater than 40 Hz significantly decreased the firing frequency and increased the burstlike activity in the firing pattern of STN neurons. An aftereffect was observed in cells that had been totally inhibited during high-frequency stimulation.⁴³ There are, however, various data that do not support an inhibitory action.^{44,45} Studies in parkinsonian primates have demonstrated increased mean discharge rates of neurons in GPi during chronic stimulation in STN. Intraoperative stimulation in human GPe has been demonstrated to improve bradykinesia by activating GABAergic fibers projecting either to the GPi or the STN⁴⁶. Thus, projection axons from neurons in the stimulated structure would be tonically activated and

would discharge independently of possibly inactivated somas, thereby increasing output from the structure during extracellular stimulation. However, long-term stimulation of a structure that would fire blanks may lead to an inactivated target.

In conclusion, the mechanisms underlying DBS therapy are unknown, and there are conflicting data suggesting inhibition or excitation of neurons. Even if local high-frequency stimulation inhibits neurons, it can also directly excite the cell and/or its axon. Therefore, the overall effects of DBS stimulation might be inhibition of intrinsic and synaptically mediated activity and its replacement by regular high-frequency firing⁴⁷. Stimulation drives neurons that behave as stable oscillators, yielding an average stable output that overrides spontaneous activity and introduces high-frequency regular spiking in the basal ganglia network. This pattern might remove the deleterious activity of the basal ganglia network, explaining the similarity between DBS and effects induced by lesioning.

High-frequency stimulation would switch off a pathologically disrupted activity and impose a new type of discharge that would be endowed with beneficial effects, perhaps by feeding the system with a synchronous high-frequency nonsignificant message.

AMOUNT OF NEURONAL TISSUE INVOLVED BY STIMULATION

The amount of neuronal tissue involved by stimulation seems rather restricted and is estimated to spread at least to 2-3 mm from the electrode if intensities in the region of 2-3 mA are used with a chronic implanted macroelectrode (2-3 V). Bipolar stimulation with 2 adjacent contacts spaced 1.5 mm apart, which would act more focally, induces about the same effect as monopolar stimulation with 1 contact but at a higher voltage. Further evidence that the effective current is localized arises from the observation of different effects obtained with 2 microelectrodes separated by 2 mm during surgery, as well as with 2 contacts of a chronic quadripolar electrode, with the middle one separated by 2-3 mm according to the electrode type ⁴⁸. The intensity of the spreading current of monopolar stimulation decreases proportionally to the square of the distance ⁴⁹. So, currents of very low intensities are recorded far from the emitting monopolar electrode but without relevant clinical effects.

ROLE OF THE NEUROLOGIST BEFORE SURGERY

The neurologist should play a major role in the management of patient candidates for DBS therapy. He or she should tell the patient objectively what to expect from DBS, what the risks are, and how to decide if and when to undergo an operation. As any probe implantation in the brain bears the risk of severe permanent morbidity in about 2% to 3% of patients, DBS should be proposed for patients with at least some difficulties in activities of daily living

or socioprofessional activities. In comparison, operating on very disabled patients who have been dependent on caregivers for many years raises enormous psychological problems in relation to creating a renewed and independent life. Moreover, severely akinetic parkinsonian patients are more at risk for general health complications in the perioperative period. Personal, social, and professional considerations, as well as how the patient copes with the activities of daily living, are all taken into account by patients and their families when deciding on a suitable time for surgery.

In the weeks before surgery, the neurologist checks for the absence of a scalp infection and for use of any drugs that favor bleeding, such as aspirin, anti-inflammatory non-steroidal drugs, anticoagulants, and lisuride. The patient should be made aware of what will happen during each step in the surgery. If operated on under local anesthesia, the patient should be prepared to participate when the site of implantation is determined during neurophysiological testing. Participation would include passive movement for evoked movement-related potentials, stimulation-induced effects on parkinsonian symptoms, and possible side effects such as motor contraction, paresthesias, eye deviation, and vegetative or emotional symptoms. An accurate report of subjective side effects by a cooperative patient helps to achieve precise targeting. Because of the risk of intraoperative psychosis and confusion, especially in parkinsonian patients, it seems wise to simplify the antiparkinsonian drug therapy. Levodopa is favored, minor drugs generally are arrested, and the dosages of dopamine

agonist drugs are decreased a few days or weeks before the date of electrode implantation, based on the drug pharmacokinetics⁵⁰.

PATIENT SELECTION

Patient selection is a critical first step as poorly chosen candidates may not have optimal benefits and have increased morbidity. Several factors must be considered before determining if a patient is an appropriate candidate for DBS surgery. A multidisciplinary approach involving the neurosurgeon, neurologist, and neuropsychologist is important to determine the appropriate surgical candidate. It is also important that the diagnosis of idiopathic PD be confirmed prior to proceeding with DBS surgery. Several neurological disorders can mimic the signs and symptoms of idiopathic PD. Multiple system atrophy⁵¹ and progressive supranuclear palsy are in the differential diagnosis that must be considered⁵². A complete, thorough neurological examination with attention to cognitive function, eye saccadic movements, postural hypotension, and postural instability, and signs of cerebellar or corticospinal involvement is important in the preoperative evaluation.

Key to this assessment is evaluating the surgical candidate in both the *on* and *off* medication states with a corroborating levodopa challenge. Perhaps the best prognostic indicator of a patient's suitability for DBS surgery is their response to levodopa⁵³.

In general, a levodopa challenge following a 12-hour medication withdrawal should provide at least a 33% improvement in the motor section of the Unified Parkinson's Disease Rating Scale ⁵⁴.

Patients who do not improve significantly with levodopa are unlikely to improve with surgery, as the therapy is largely aimed at increasing *on* time and decreasing *on-off* fluctuations. The levodopa challenge is also useful to demonstrate to the patient and family the extent that the parkinsonian symptoms are likely to improve after surgery. Patients should be educated not to expect an improvement in function greater than the best *on* medication period with the concomitant reduction in drug-induced dyskinesias. Tremor is an exception and can improve with STN DBS even if not significantly affected by levodopa. Patients should be advised that axial and gait symptoms are less likely to be impacted than appendicular symptoms. One of the most important presurgical assessments is the neuropsychological evaluation. Deep brain stimulation for PD does not seem to cause permanent cognitive changes. However, patients who present with cognitive decline preoperatively tend to be poor candidates and may worsen after surgery. A staged procedure is a good alternative to simultaneous bilateral surgery in elderly patients with borderline cognitive function ⁵⁵.

Severe anxiety may become a major impediment for awake stereotactic surgery, especially in prolonged operations. Counseling prior to surgery might be helpful.

UNIVERSITY OF FLORIDA MNEMONIC DEVICE FOR PATIENTS

WITH PD CONSIDERING DBS ⁵⁶ [DBS IN PD]

Does not cure.

Bilateral DBS is often required to improve gait, although sometimes unilateral DBS has a marked effect on walking.

Smooths out on/off fluctuations.

Improves tremor, bradykinesia (slowness), stiffness (rigidity), and dyskinesia in most cases, but may not completely eliminate them.

Never improves symptoms that are unresponsive to your best “on.” For example, if gait or balance do not improve with best medication response, it is very unlikely to improve with surgery.

Programming visits are likely to occur many times during the first 6 months, and then follow-up visits as frequently as every 6 months. There will be multiple adjustments in the stimulator and in the medications.

Decreases medications in many, but not all patients.

PREOPERATIVE MANAGEMENT

Full medical assessment: The risk of discontinuing medications that affect anticoagulation and platelet aggregation should be weighed against the potential benefits in the quality of life offered by DBS surgery. However,

timely discontinuation of these latter medications is mandatory for stereotactic surgery since intracerebral hematomas are the most serious of all potential complications from DBS. Any anticlotting medications, including aspirin, ticlopidine, clopidogrel, and all nonsteroidal anti-inflammatory drugs should be discontinued at least 7 to 10 days preoperatively to ensure the return of normal blood clotting function.

The night prior to DBS surgery, the antiparkinsonian medications are typically held to pronounce the Parkinson's symptoms at the time of surgery. Patients should be willing and able, both physically and cognitively, to undergo an awake surgical procedure requiring several hours of immobilization in a stereotactic frame. The patient and family must be willing and able to bear the responsibilities for maintaining a chronically implanted hardware system. The DBS surgical candidate must be educated regarding environmental concerns with implanted hardware.

Patients with DBS hardware should not be exposed to large magnetic fields. Compatibility exists with only a limited number of magnetic resonance (MR) sequences in machines that have undergone safety testing. Individuals with other health issues that may require frequent MR imaging may not be ideal candidates for DBS. Body coils are particularly dangerous for DBS systems and their need may pose a contraindication for patients with spinal disease that require future MRIs. Unfortunately, the association of spinal problems with medically refractory Parkinson's disease is not uncommon and it

may be necessary to judge along with the patient and family which disease should be prioritized.

Finally, DBS implantation should be regarded the first step in an extended management plan. The caretakers and the patient should be committed to treating the patient within the specialized center for programming, and hardware management issues (such as the need for battery change) in the near and long term.

SURGICAL PROCEDURE

APPLICATION OF HEAD FRAME AND IMAGING

Surgical strategies and details of procedure vary with the surgical teams, the equipment they are used to, and the local healthcare system constraints. Stereotactic surgeons typically master the use of their institution's equipment of choice, which are used for a variety of stereotactic procedures. Among them, DBS is probably one of the most technically challenging and should not be considered a beginner's procedure. A variety of head frames can be used such as the Leksell, CRW, Riechert- Munding, and other commercially available systems.

Placement of the head frame should be done as close as possible to surgery in order to minimize the duration of discomfort and risk of displacement. It is important when attaching the frame to the patient's head to

avoid any rotation or tilt of the head relative to the frame axes. The base of the frame should be placed parallel to a line extending from the lateral canthus/orbital floor to the tragus in order to parallel approximately the anterior commissure–posterior commissure (AC–PC) line. Ear bars (with ear plugs placed for patient comfort) may be used to balance the ideal position of the frame while applying the pins.

Ideally, the head should be centered in the frame, so that the midline falls within the center point of the stereotactic space defined by the head frame system. Care must be taken such that the edges of the frame should never be in contact with the nose or the occipital/neck area due to risk of skin erosion, which could be encountered during an extended stereotactic procedure. The frame should not obscure the patient's eyes since this makes communication with the patient and assessment of eye movements more difficult during surgery.

PLACEMENT OF PINS

The scalp is shaved and prepared with betadine and the pins are inserted under local anesthesia of preference, typically lidocaine and/or marcaine. A small dose of intravenous midazolam or other sedation can be given prior to insertion of the pins in order to minimize awareness and memory of frame placement. The anterior pins can be placed two finger breadths above the orbital rim, taking care to avoid the supraorbital nerve. Posteriorly, pins should

be located so as to avoid penetration of the cerebral venous sinuses. The height of the base of the frame must also be taken into consideration so that prospective targets lie comfortably within the frame's coordinate system, avoiding the extremes, which will mechanically hamper positioning the arc for targeting. In addition, since the pins can create significant artifactual distortion of CT imaging, they should be placed such that they distort neither the AC, PC, nor the target. The pins should firmly purchase the outer layer of the skull to prevent the frame from being displaced during a prolonged surgery. After application of the frame, an attempt should be made to move the patient's head and stress the pins. Any perception of pain by the patient at this point might imply inadequate insertion of the pins.

Patients with severe anxiety or low tolerance to pain may not tolerate awake placement of the head frames. In those instances, the head frame may be placed under heavy sedation or general anaesthesia.

IMAGING FOR TARGETING

Once the frame is placed, the patient is taken for preoperative imaging. CT, MRI, and ventriculography can all be used to construct the stereotactic imaging database required for DBS implantation.

For decades, stereotactic ventriculography was used to identify the AC and the PC. To avoid parallax effects, ventriculography was ideally performed with fixed X-ray tubes with long projection lines (teleradiology). Today,

ventriculography has been replaced by stereotactic computed tomography (CT) or magnetic resonance imaging (MRI).

The CT scan should include the upper portion of the frame, the anterior and posterior limits of the frame, and vertex up to the skin edge in order to encompass all the fiducials. The slices are optimally obtained with the thinnest slice thickness with no gap between slices. If dislodgment of the frame occurs after the volumetric stereo CT, the entire procedure has to be restarted due to the loss of relationship between the fiducials and intracranial structures.

Volumetric, gadolinium-enhanced, T1-weighted MRI, T2-weighted images, or inversion recovery images can be obtained with the head frame on, or preoperatively to expedite the process on the day of surgery. T2 and inversion recovery images are beneficial for direct targeting of the structure of interest and surrounding areas.

Often, excessive tremor hampers the interpretation of the preoperative MRI, and another one may be obtained with the head frame on, which helps to stabilize the head during image acquisition.

While MRI has superior soft-tissue resolution, CT is less susceptible to the distortional artifacts produced by the inhomogeneities in the magnetic field and thus more accurately represents the actual position of intracerebral structures in space. Consequently, reliance on image fusion and merging will allow for visualization of multiple imaging data sets.

The chief advantages of MRI include a noninvasive imaging modality, better resolution of the deep and superficial cerebral structures, and planning of the entry point ⁵⁷ Because of the problem of MRI distortion, many centers use MRI coregistered to CT ⁵⁸.

It has been demonstrated that CT- and MRI-guided localization of the commissures is accurate and even superior to ventriculography ^{59,60}. The most important drawback to MRI is the potential for image distortion.

CT is considered the most geometrically accurate imaging modality for stereotactic localization. CT imaging, compared to MRI, has the relative disadvantage of being inferior in the display of anatomic details. The geometric accuracy of magnetic resonance scanning can be comparable to that of CT scanning when gradient and magnetic field inhomogeneities are corrected. Under optimal conditions, the average difference in size between CT and MRI stereotactic coordinates of external fiducials, intracerebral target points, and anatomic landmarks is in the order of 1 pixel. Both with CT and MRI stereotactic imaging, it is important to obtain 1 mm or at least 2 mm axial scans through the third ventricle and the basal ganglia region. The imaging data can be transferred to a workstation where the axial scans are displayed simultaneously with coordinated reformatted sagittal and coronal images. The simultaneous and multiplanar display allows visualization and accurate confirmation of the localization of the commissures in 3 planes. Misalignment

of the intercommissural line with regard to the 3 orthogonal axes of the stereotactic frame must be considered and corrected appropriately ⁶¹.

T2-weighted images with a long acquisition time are better for STN visualization ^{62,63,64,65,66}.

T2-weighted images show that the red nucleus (RN), the substantia nigra (SN) and the STN are relatively hypointense as compared to surrounding structures, although this signal does not perfectly fit with the anatomical structure ⁶⁷. The use of the red nucleus as an internal fiducial marker for directly targeting the optimal region of STN stimulation was found reliable and approximates by more than 3 mm the position of the electrode contact that provides the optimal clinical results ⁶⁸.

Comparison of direct targeting and final MER-determined coordinates showed unacceptable distance errors of 2.6-3.9 mm ^{69,70}. Thus, although direct targeting may be helpful, it can yield coordinates at some distance from the final MER target.

Since 2 MER tracks separated by 2 mm usually provide totally different results, in recordings as well as in clinical benefits or side effects induced by stimulation, precision within 1 mm is needed.

Neurosurgeons do not exactly target where they intend to target with changes of about 1 to 3 mm. Teleradiography shows that even removing the

style of the Medtronic electrode frequently induces a 1 mm displacement of the electrode, proving that the insertion of a stiff probe in a soft structure bathed in fluid, such as the brain, induces a slight shift despite the most accurate targeting. That is why functional electrophysiology is mandatory for achieving the precision necessary for optimal therapeutic benefit.

TARGET SELECTION

Centers use various combinations of anatomical targeting strategies. One can target using an indirect method that involves reformatted anatomical atlases as well as formula coordinates based on known distances from the

AC and the PC landmarks. The STN and GPi can also be chosen on the basis of direct targeting by visualizing the structure on T2 and inversion recovery images. With current imaging limitations, Vim can only be targeted indirectly and confirmed with intraoperative physiological data.

DIRECT TARGETING

Direct targeting is based on MRI visualization of the structures. A target within STN can be chosen at the ventral part of the somatosensory STN, which is the lateral part of the nucleus. The axial and coronal T2 images are particularly important for adequate visualization of the STN as a sharp contrast can often be seen between the nucleus and the surrounding white matter.

The red nucleus can also be clearly seen and the STN lies anterior and lateral to the red nucleus. The anterior border of the red nucleus can be used as a landmark for the anteroposterior localization of the STN target ⁶⁸. This is best visualized in the axial T2 images.

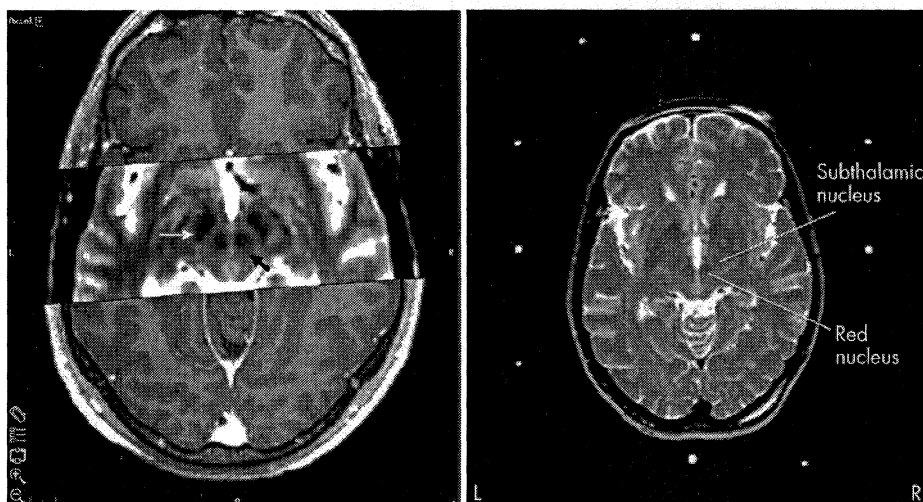


Fig. 1 Direct STN targeting. Axial T2-weighted image showing the subthalamic nucleus (white arrow) anterior and lateral to the red nucleus (black arrow). Anterior border of the red nucleus aligns with the posterior third of the STN. The T2 images are crucial for the direct targeting of the STN .

INDIRECT TARGETING

Indirect targeting is based on a standardized stereotactic atlas and on a formula-derived method based on AC and PC landmarks. While atlas-based coordinates are biased by the inherent inaccuracies of atlases, coordinates can be derived from the experience of teams and represent the average values of the coordinates of these best contacts, gathered in a rather large number of cases.

Referring these coordinates to internal landmarks such as AC–PC length and height of the thalamus above the AC–PC plane provides normalized coordinates less dependent on individual variations. The formula uses the midcommissural point (MCP) or the PC as reference, which is calculated after selecting the AC and PC coordinates. Typical initial anatomical coordinates for the ventral and sensorimotor STN are 11 to 13 mm lateral to the midline, 4 to 5 mm ventral to the intercommissural plane, and 3 to 4 mm posterior to the MCP.

These coordinates may not represent the ideal location for implantation but are used as initial anatomical targets, which are verified by physiological recordings.

Indirect targeting has been the traditional method in stereotactic neurosurgery. The limitation of this method is that it does not take into account the discrete anatomical variations among individuals. Not all brains correspond to the topographical distribution depicted in a given atlas. Even the reformattable atlases available in computerized planning stations may not conform adequately to the patient's anatomy. In this sense, direct targeting seems to have obvious benefits over indirect. It is based on the imaging data set of the individual's own anatomy. Imaging techniques have advanced dramatically, allowing for adequate visualization of the STN in T2 images. However, several pitfalls exist, such as failure of fusion between CT scans and MRI or magnetic distortions that may alter the geometry of the nucleus. At the

current stage, it is best to perform all targeting methods and correlate them prior to surgery.

ENTRY POINT SELECTION

It is necessary to find an approach that will best facilitate interpretation of microelectrode recordings while concomitantly maximizing safety. From an electrophysiological mapping standpoint, a parasagittal approach is preferable but not feasible in all cases. Entry points are chosen based on the patient's anatomy to provide a safe and optimal trajectory through the areas of interest. Typical angles of approach for the STN target are 15 to 30 degrees from the sagittal plane and 50 to 70 degrees in the anterior-posterior direction. The precise entry point may be refined on the planning console such that the trajectory passes through the crown of a gyrus rather than into a sulcus. This avoids inadvertently damaging sulcal or pial vessels, which lie on the cortical surface. The cortical vessels should be avoided as well as the sulcus. After selecting preliminary entry points, the images can be reformatted to the trajectory view, which provides three orthogonal planes positioned with respect to the trajectory rather than the patient's anatomy.

The approach then may be traced at millimetre intervals to ensure that no deep sulci are transgressed and that the ventricular ependyma is not scythed. A typical approach will pass the electrode to course through the anterior portion of the thalamus, zona incerta, subthalamic nucleus, and substantia nigra. Any

given trajectory must be altered to avoid major visualized vascular structures. Venous tributaries draining into the superior sagittal sinus or branches of the anterior cerebral artery may limit a more medial approach. Enlarged ventricles and the presence of ependymal and intraventricular veins may also force the entry point to be moved laterally, at the expense of missing the thalamus and consequently the transition to zona incerta in STN surgery.

Gadolinium enhancement of the T1-weighted images allows visualization of vessels that would otherwise be unnoticed. It is clear that accounting for these vessels minimizes the risk of hemorrhage, although other groups report a low rate of bleeding without this method⁷¹.

POSITIONING AND ANESTHESIA

The patient is positioned supine on the operating room table, with the knees flexed and the head of the table elevated to various degrees depending on surgeon preference.

The head frame is fixed to the table with an adapter to the table or the floor. The patient's feedback is used to find a neck position that will best tolerate extended immobility. Certain teams use intravenous sedation for the incisions and bony opening until electrophysiological mapping begins. Although sedation can be used, there is a potential risk for interference with microelectrode recording. Agents such as propofol are quickly reversible and may be preferred over other longer-lasting agents. Careful control of the

arterial blood pressure is maintained to minimize the risk for intracranial bleeding. Patients with labile blood pressure may benefit from invasive monitoring for enhanced titration of the antihypertensive drugs. Preoperative antibiotics should be administered before incision and repeated thereafter. Draping should be performed to allow visual access to the patient's face, arms, and legs while maintaining a sterile surgical site.

STEREOTACTIC APPROACH

The coordinates for the X, Y, and Z coordinates are set and the entry points and the midline are marked on the skin and the incisions are planned. The stereotactic arc can be used to mark precisely the incision and the burr hole site, taking advantage of the trajectory planning. Depending on the thickness of the skull, the inner rim of the burr hole will limit the progression of the cannulas if the hole is drilled perpendicular to the skull surface. In order to prevent this problem, the holes should be drilled in the axis of the trajectory, at the same angle chosen for the stereotactic approach. It is worthwhile to start implantation on the side contralateral to the patient's worst symptoms in case the patient does not tolerate a bilateral procedure.

The dura mater, arachnoid, and pia mater on the first side are coagulated and opened. Some teams do not open the dura and insert the tube guide by puncture of the dura, thus preventing subdural air penetration and CSF leakage. At this point, sedation can be interrupted to allow the patient to be awakened

for microelectrode recording. The cannula is inserted for microelectrode recording to a predetermined dorsal offset to the chosen anatomical targeting. A hydraulic or electrical microdrive is used to advance the microelectrode in submillimetric steps. Except when dura is not opened, either gelfoam and/or fibrin glue is placed around the cannula in the burr hole to provide a seal, thus minimizing CSF loss and pneumocephalus.

ELECTROPHYSIOLOGICAL MAPPING

To identify the physiologically optimal target for DBS, MER may be employed in a multitude of ways, according to the experience of each group. Without any doubt, in experienced hands, microrecording can precisely define the boundaries of the target^{72,73,74,75}. The microelectrode goes through the main part of the neuronal structure. Since the anatomically precise determination of a target can be off by a few millimeters, some groups use a device allowing 5 simultaneous parallel trajectories in a concentric array, with 4 outer electrodes being separated by 2 mm from a central electrode aimed at the theoretical target. Two to 5 microelectrodes are generally located in the target, but they were eventually replaced by the chronic Medtronic electrode, because it provides better results than the others. Using this device (the so-called Ben's gun) provides the advantage of comparing the effects of each electrode side by side and ensuring that the chronic electrode will be placed exactly at the same location as the microelectrode.

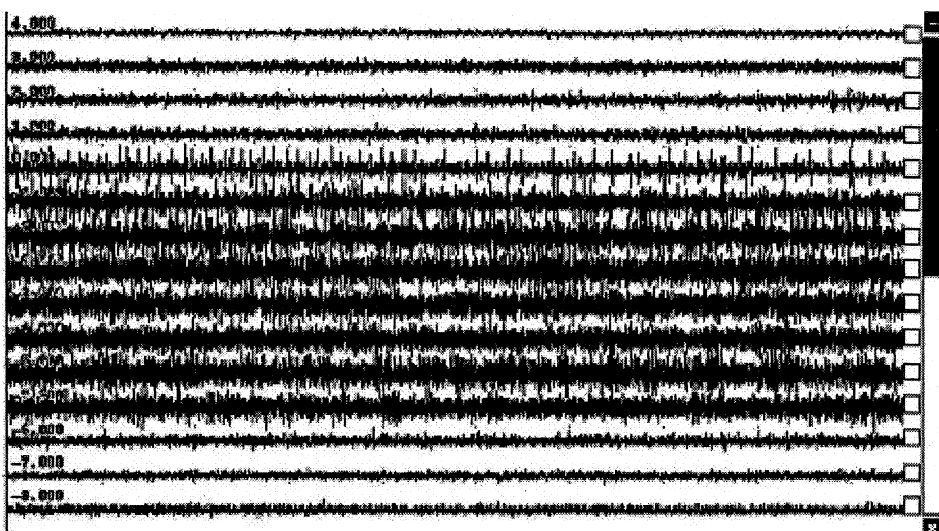


Fig 2. A typical STN recording (25.000 mm to 0.000 mm) showing the irregular pattern of discharge with spikes of different sizes, occurring at random intervals.

RISK OF BLEEDING DUE TO MICROELECTRODE RECORDING

Although MER being the cause of increased intracranial bleeding or contusion remains a controversial matter^{76,77,78,79,80}, it seems obvious that the risk of bleeding or contusion increases as the number of trajectories performed to delineate the target increases. A twice higher rate of hemorrhage in cases performed with MER as compared to macrostimulation alone has been reported. In Palur et al. meta-analysis⁸¹ it was noted that non-MER techniques were at least 5 times less likely to have hemorrhagic complications⁸². In 2001, the DBS Study Group found that the number of microelectrode passes used to determine target location correlated with the risk of hemorrhage. However, the overall risk of bleeding in both MER and non-MER groups is relatively low, with an occurrence of 1% to 8% of cases^{81,82,83}.

Although the usefulness of MER may remain debatable, the use of stimulation in a nonanesthetized patient is necessary to localize the optimal target site.

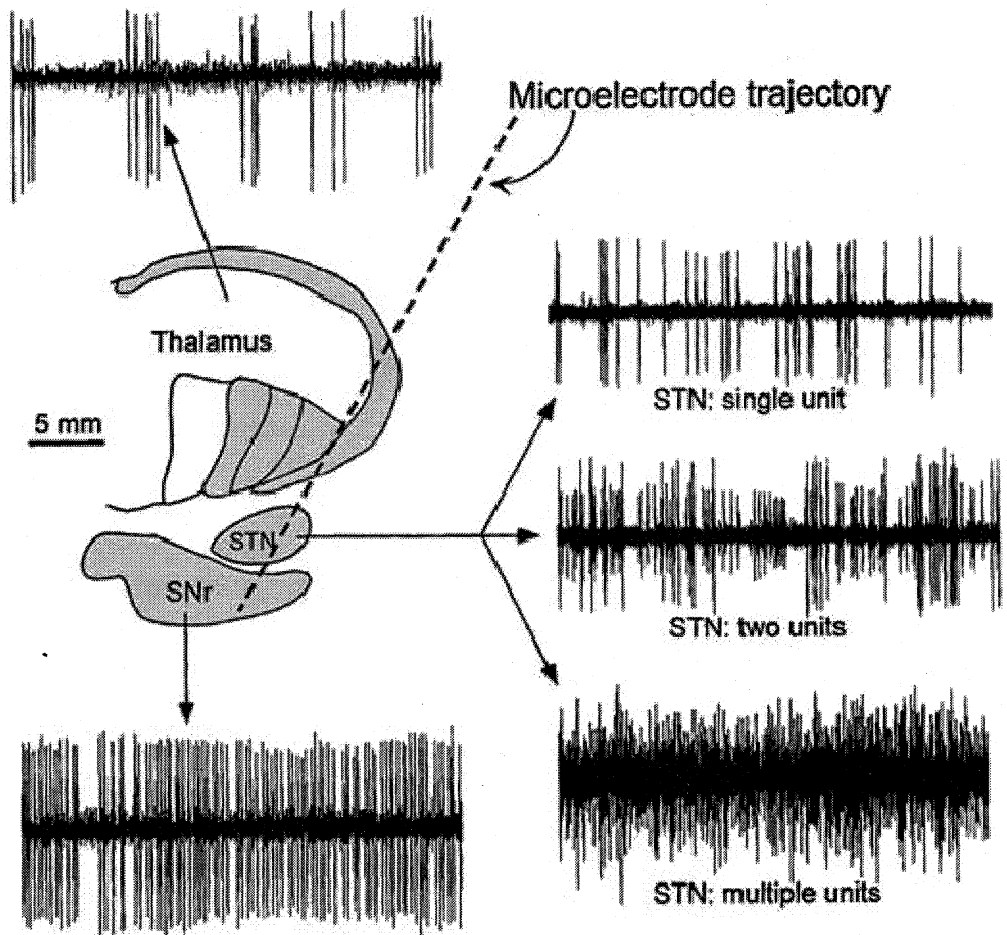


Fig. 3 Representative MERs in various nuclei along a trajectory (dotted line) through the STN. Each trace is 1 second long. Upper Left: Dorsal thalamic bursting cell. Right: Three recordings made in the STN. Lower Left: Recording made in the Substantia nigra (SNr).

INTRAOPERATIVE STIMULATION

Testing the DBS electrode for efficacy and side effects is most commonly performed by all teams. However, certain groups rely extensively on the microelectrode recording and stimulation. In STN surgery, reduction in tremor, rigidity, and bradykinesia is expected during intraoperative macrostimulation. Particular attention should be directed to determination of side effects, including corticospinal activation (upper extremity, lower extremity, and face/tongue), speech changes, conjugate (corticospinal activation) and dysconjugate (activation of the third nerve) eye deviation. For STN targeting, paresthesias may indicate a more posterior implantation of the lead and, if transitory, are not considered a contraindication for implantation. A well-targeted electrode typically allows stimulation up to 4 volts without causing side effects. Lower thresholds indicate that the lead may be close to other structures and may have to be repositioned.

If side effects are found at thresholds lower than expected, repositioning of the electrode will be necessary. It is advised to move by more than 2 mm, as the risk of the electrode falling into the previous tract is high. It should also be noted that multiple macroelectrode penetrations may create fluid-filled spaces that may cause stimulation to spread unpredictably and result in unreliable macrostimulation. These problems are reduced by procedures using simultaneous insertion of several microelectrodes.

Most groups find that their judicious use in the operating room may confirm optimal targeting and help avoid side effects due to chronic stimulation. In the suitable implantation site, high-frequency stimulation induces motor benefit at low intensities, as well as no side effects or side effects at far higher intensities in a patient under local anesthesia.

The Paris group found suboptimal results in a group of PD patients operated on for STN stimulation under general anesthesia in comparison with the group under local anesthesia⁸⁴. General anesthesia allows assessment solely of motor contraction related to pyramidal tract stimulation. General anesthesia should only be used in patients with severe abnormal movement, such as some generalized or cervical dystonia or Tourette's syndrome. Generalized anesthesia may also be necessary for anxious or phobic patients, and the evaluation of neurological symptoms and signs. The neurologist who evaluated the patient candidate preoperatively for surgery seems to be the person most prepared for intraoperative testing.

In summary, and concerning the most frequent type of DBS (i.e., STN stimulation for PD, at the sites where microelectrode recordings show neuronal discharges characteristic of the STN), electrical high-frequency stimulation induces a dramatic improvement in parkinsonian motor symptoms at low intensity and side effects at high intensity (wide therapeutic window). The amelioration of the symptoms can be accompanied by dyskinesias, which are a

positive predictive factor for the outcome. The other unpleasant effects are induced by stimulating the surrounding areas of the STN.

DBS ELECTRODE IMPLANTATION

Various implantation approaches are used, from placing the active contacts in the center of the nucleus, at the ventral border, beyond the ventral border, or spanning multiple areas as determined by the team. After the optimal location for implantation of the electrode has been decided, the DBS lead (macroelectrode) can be implanted.

DBS ELECTRODES

The two commercially available electrodes have four contacts of 1.5 mm height and 1.27 mm diameter and differ only in the spacing between contacts: 1.5 mm in the 3387 model and 0.5 mm in the 3389 model (Medtronic, Minneapolis, MN).

Contact 0 (the contact at the electrode's tip) can be positioned at the physiologically defined ventral border of the nucleus and the remaining contacts will span for 10.5 mm (3387) or 7.5 mm (3389) in the trajectory.

The reduction in overall span of the contacts from 10.5 mm to 7.5 mm seems reasonable given that in VIM, GPi, and STN the length of the efficient target region is less than 7.5 mm. Therefore, the model 3389 lead increases the spatial and stimulation resolution. The longer interval afforded by the model

3387 lead allows stimulation of a greater region outside the theoretical target and offers greater ability to compensate for a misplaced lead with regard to depth along the track. There are no data that directly compare the 3387 and 3389 models. The middle of the 4 contacts of the DBS electrode (between contacts 1 and 2) is positioned in the middle of the determined target for the VIM and STN .

When an inserting cannula is used, the chosen electrode is loaded in such fashion that the first contact (and not the dead space at the tip of the electrode) is aligned with the tip of the cannula. Other systems may have different loading structures, depending on the distances between the electrode holder and the offset to target.

Fluoroscopy is used by many centers to monitor DBS lead movement and migration. Some centers perform AP and lateral X-rays while others perform lateral only. In dedicated stereotactic operating rooms, the X-ray tubes and the frame are part of a solid-state setup, which avoids the instability of portable X-ray system alignments.

The patient is examined for baseline tremor, rigidity, and bradykinesia. The microdrive can be used to advance the electrode to the desired target or, alternatively, manual advancement can be performed to the target. Fluoroscopy can be used to confirm that the electrode is assuming a straight trajectory. A microsubthalamotomy, thalamotomy, or pallidotomy effect may occur

secondary to the mechanical insertion of the electrode, with improvements in PD symptoms.

SECURING THE ELECTRODE

Once the DBS electrode is implanted at the final location, it must be secured in place while removing the cannula, carrier, and microdrive. Continuous fluoroscopy is helpful to monitor the potential of electrode displacement.

Anchoring and securing the lead can be achieved by various techniques depending on the center preference and expertise. These include securing the lead to the skull with ligature embedded in dental cement, miniplates, and screws, the Medtronic burr hole ring and cap.

Advantages and disadvantages exist to each of these methods. Dental cement and miniplates are not recommended by the lead manufacturer. Their use may be necessary in peculiar scenarios such as when a craniectomy has to be added to the burr hole due to unexpected findings and the burr hole rings will not conform to the opening in the skull.

The burr hole ring that is provided by the lead manufacturer can be safely used but a tendency exists to drive the electrodes deeper when inserting the cap. This can be easily observed on live fluoroscopy. The Stim-Loc device

provides good stabilization of the electrodes without a tendency to push the electrodes deeper. It is a costly tool that may not be accessible to many centers.

No electrode migration on large series of patients has been reported with the cement or plate and screw method ⁸⁵ in contrast to the Medtronic cap ⁸⁶ . It is recommended that fluoroscopy be used to protect against lead migration during fixation, especially when using a cap.

Once secured, the lead is attached to an extension wire that is tunneled to the parietal/occipital region. The excess lead can be coiled around the burr hole device or along the path of tunneling to serve as strain relief. The burr hole and the wound should be thoroughly irrigated with rinsing solution before closing the skin. Depending on the time that will be allowed between implantation of the electrode and the pulse generator in a staged procedure, scar tissue can form around the excess wire and burr hole device. In manipulating the DBS lead, sharp instruments or instruments with “teeth” should always be avoided since insulation may be inadvertently damaged.

IMPLANTATION OF PULSE GENERATOR (IPG)

This is the last step of surgery and is performed under general anesthesia. It can be performed the same day or in a delayed/staged fashion(over a 1- to 4-week period). Due to the long duration of the procedure and the need for general anesthesia, IPGs can be implanted several days after

the DBS lead implantation when the patient has recovered from the intracranial procedure.

Staged surgery has its advantages. In particular, it makes it possible to avoid a lengthy surgery for electrode implantation and to check electrode location with a postoperative MRI before IPG implantation. For IPG implantation, the patient is positioned supine, with the head turned to the opposite side of the intended site of IPG implantation. Preoperative antibiotics are again administered 30 minutes prior to incision. A subcutaneous pocket is then created for the IPG and this pocket is connected to the DBS lead tunneled previously to the parietal/occipital region. The most common location for the IPG placement is infraclavicular and typically marked 2 cm below the clavicle and 4 cm away from the midline or 2 cm away from the lateral manubrial border. However, certain patients may require placement in other locations due to body habitus (very thin patients), age (pediatric patients), a history of prior surgery in the region, or vanity. In addition, certain activities such as hunting require the use of the chest to stabilize equipment. The IPG should be placed in a location that minimizes pressure and trauma to the unit.

Anecdotal reports cite local trauma as an infection risk with other implanted hardware systems. Other locations include the subcostal area and the flank as well as the lumbar region and buttocks. Regardless of the location, it is useful to mark the incisions before the final patient position to achieve maximal symmetry and cosmetic appeal. Marking the subclavicular incision in women

deserves special attention for cosmesis. It may be useful to mark the incisions in the standing or sitting positions in order to best predict the final location of the incisions and generators. In most individuals, it is possible to create a subclavicular sub-cutaneous pocket that is deep enough for hardware implantation, just against the pectoral aponeurosis. In very thin patients, it may be necessary to create the pocket in between the pectoralis muscle and its fascia, although extra care must be taken as an increased risk for postoperative hematoma formation may exist. Additionally, for implantation of the IPG in a nonsubclavicular area, utmost care should be taken to prevent approximation of the IPG to any bony prominence such as the rib or the iliac crest. A small parietal/occipital incision allows identification of the connector that protects the DBS electrode. Externalization of the lead must be carefully performed since it can be tethered by scar tissue formation. Excessive force should be avoided to prevent breakage of the electrode or migration of the intracranial portion. A tunnel is created from the parietal region to the IPG pocket and the 51 cm implantable extension wire is passed and connected to the distal aspect of the DBS lead and IPG. The connector is internalized and pulled distally but should never be placed at the level of the neck below the mastoid, where mobility tends to cause tethering and resultant hardware failure can occur. A good position for the connector is the retroauricular region. When located too medially, it can cause pain when sleeping supine and may come in contact with the lesser or greater occipital nerves. If located too laterally, it may cause

discomfort while wearing glasses. Some teams place it higher on the head, at the upper part of the temporal muscle. The excess extension lead is coiled behind the generator and the IPG is anchored to the fascia with nonabsorbable sutures. Anchoring of the generator to subcutaneous fat should be avoided since caudal migration may occur due to the weight of the IPG. Closure is performed in layers after copious irrigation.

The disadvantages to this system include the greater volume that may impose a risk of erosion in very thin patients and the limitation to a single set of pulse frequencies.

Currently, two models of IPG are available: the single-channel Soletra and the dual-channel Kinetra. The Kinetra is a larger device that can be used to control two DBS electrodes, thus allowing for a single-side IPG implantation. It is close to twice as large as the Soletra but requires only one implantation site and one subcutaneous tunneling pass ⁸⁷. In addition, there are other advantages, such as the absence of a current-multiplier circuit over 3.6 V, which lengthens battery life in high-voltage situations and makes the device more insensitive to magnets, which together prevent insensitivity to magnets, which prevents inadvertent arrests, the most frequent side effect of the Itrel/Soletra. However, it seems that the increased size and weight of the Kinetra, compared to the Soletra, lead to a trend toward a higher rate of adverse surgery-related events.

POSTOPERATIVE MANAGEMENT

In the immediate hours after surgery, it is important to keep arterial blood pressure in the normal range. In addition, the patient's preoperative PD regimen should be restarted immediately after surgery to avoid problems with dopaminergic withdrawal. Patients should undergo postoperative CT scans and/or MRI scans to assess the electrode location and intracranial status. In addition, plain X-rays are obtained to assess the location and geometry of the leads and hardware. Parkinson's medications may need to be adjusted depending on the patient's status. Cognitive and behavioral changes may occur in the postoperative period, particularly in older patients. Patients can be discharged as early as 24 hours after surgery, depending on their neurological and cognitive status.

The subthalamic nucleus is a very small target. With correct electrode localization, all parkinsonian signs are improved using relatively small current amplitudes. On the other hand, this small target is surrounded by corticobulbar, corticospinal, oculomotor, sensory, and autonomic fibers. Whereas these eloquent structures are helpful during intraoperative targeting, misplaced electrodes can lead to side effects related to these bypassing fibers. Moreover, due to their small size, the motor, associative, and limbic territories of this target are close, explaining some of the potential effects and side effects on mood and behavior specific to the target. Stimulation of electrodes that are perfectly located within the sensorimotor part of the STN will lead to

stimulation-induced dyskinesias, especially if levodopa-induced dyskinesias are severe before surgery⁸⁸. Although dyskinesias induced by STN stimulation predict a good long-term outcome⁸⁹, in the short term such dyskinesias can be difficult to handle and require major changes in dopaminergic medication. management of patients with subthalamic stimulation is more complicated and more time-consuming in the postoperative period compared to other targets. However in the long term, the effects seem more stable^{71,90} and this justifies the choice of this complex target, in addition to prompting a better antiakinetic effect, lower energy consumption, and the possibility of sparing medication³². A further advantage may be the possibility of improving levodopa-induced behavioral side effects in the long term, an indirect benefit that is related to the possibility of reducing dopaminergic medication⁹¹. So-called apraxia of eyelid opening, a bilateral involuntary closure of the eyelids without the lowering of the eyebrows, is typical for blepharospasm, mainly characterized by prolonged effort to reopen the eyelids with visible contraction of the frontalis muscle, and one of the most frequent side effects of subthalamic stimulation⁷¹. This side effect is related to lateral current diffusion to the corticonuclear fibers to the facial nerve to the upper part of the face⁹². About half of the fibers to the upper part of the face descend to the ipsilateral facial nerve, the other half cross contralaterally. For this reason, side effects related to current diffusion are bilateral in the upper part of the face, whereas they are almost exclusively found contralaterally in the lower part of the face, manifesting mainly as

perioral contractions. This apraxia of eyelid opening shows a good response to pretarsal injections of botulinum toxin ⁸⁸. Dysarthria can be a side effect of subthalamic stimulation related to lower facial contraction but also to diffusion to the laterally located corticobulbar fibers, the latter inducing dysarthria without clinically detectable muscle contractions.

Diplopia related to adduction of the ipsilateral eye that can be accompanied with downward or more rarely upward deviation, sometimes also with a widening of the ipsilateral palpebral fissure, is a sign of current diffusion to the third cranial nerve from electrodes that are located too medially and too caudally. Using bipolar stimulation of electrode contacts that are located more dorsally may help to avoid this side effect.

Contralateral paresthesias is a common side effect related to posterior diffusion to the medial lemniscus. This side effect tends to disappear rapidly with chronic stimulation.

Weight gain is the most common side effect of subthalamic stimulation. Patients gain on average 5 kg. They should be informed about potential weight gain before surgery and encouraged to lose weight if they are obese before surgery. Nutritional counseling can be useful, especially for those patients who gain more than 3 kg within the first 3 months after surgery and who tend to be overweight.

Many behavioral problems have been reported in PD patients after surgery. However, PD is a neuropsychiatric disorder ⁹⁴ and most of the postsurgical behavioral disorders can be explained by preexisting personality disorders and decompensation of previous psychiatric disorders ⁹⁵. The most common problem encountered is postoperative transient confusion ⁷¹ with or without psychosis, which may require transient treatment with clozapine in case of relevant hallucinations, delusions, or agitation. Both levodopa and subthalamic stimulation do have psychotropic effects in addition to the motor effects. An excess of treatment (levodopa and stimulation) will lead not only to dyskinesias but frequently induces hypomania or even rarely can lead to full-blown manic states ^{96,97}. To the contrary, if the dopaminergic treatment is reduced too much, dyskinesias disappear and an apathy inherent to PD is frequently unmasked ⁹⁸ requiring another increase in dopaminergic treatment ⁹⁹. Apathy frequently appears as an isolated problem without depression ¹⁰⁰ and generally responds to dopaminergic treatment. In the long term, however, apathy is the most frequent behavioral abnormality. Depression also has been described after surgery ^{101,102,103,104}. Depression can be reactive in a population at risk, whereas depression can also appear in the context of dopaminergic withdrawal, and this depression can also respond to an increase in dopaminergic medication ⁹⁹.

Suicide has been reported after surgery¹⁰⁵. Risk factors for suicide are preoperative depression and repeat surgery, indicating a selection bias. The prevalence of depression in typical surgical candidate was found to be 60%¹⁰⁶.

In conclusion, it seems obvious that PD patients do require a modulation of their dopaminergic treatment not only in response to their motor state, but medication also must be adapted to mood and behavior¹⁰⁶. Furthermore, factors related to psychosocial adjustment must be taken into account, including psychological and reactive changes in response to motor and functional changes, unrealistic expectations, limited social support, changes in identity or interpersonal relationships, or the loss of the role of the patient within the family¹⁰⁷.

POSTOPERATIVE IMAGING

Postoperative imaging is invaluable for documenting the absence of complications and the location of the electrode. The latter is useful for interpreting the clinical results of stimulation and for troubleshooting. Following insertion, the location of the lead should be confirmed by imaging¹⁰⁸. This may begin with intraoperative fluoroscopy or stereotactic X-rays. Most centers perform a postoperative imaging study consisting mainly of MRI. Yelnick et al.¹⁰⁹ have quantified the artifact created from a model 3389 lead. They show that the model 3389 electrode has an artifact on MRI of 3.5 mm in diameter instead of 1.27 mm and that the 4 contacts span 10.7 mm instead of

7.5 mm. The center of the artifact they reported concurred with the center of the electrode. A number of centers fuse the postoperative imaging study to the preoperative stereo MRI or CT to assess the final DBS electrode positioning¹¹⁰ Postoperative T2-weighted MR images to localize STN also have been used.

Postoperative MRI before IPG implantation is safe. After implantation of the complete DBS system, potential MR-related complications include electrode or pulse generator movement or heating¹¹¹, the latter of which may result in an intraparenchymal lesion. No device failures were found as a result of postoperative MRI¹¹². However, heating at the lead tip may result in serious injury to the patient and it is therefore necessary to follow safety recommendations strictly^{113,114}.

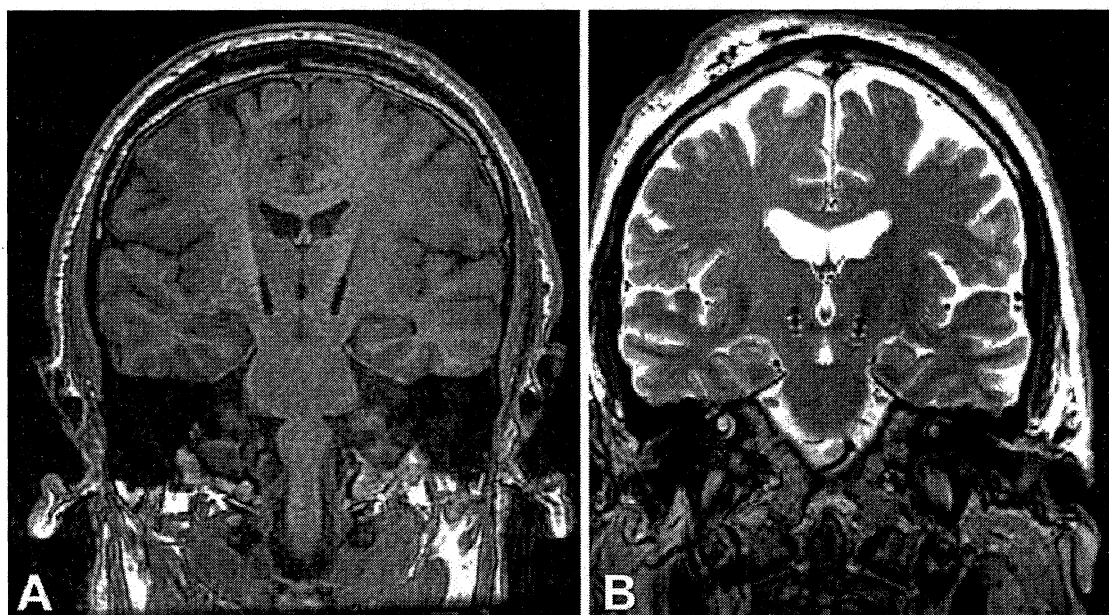


Fig 4. Postoperative T1- and T2-weighted MRIs from two different patients after bilateral STN DBS surgery. Electrodes are located just lateral and anterior to the nucleus (A and B)

A study by Ruth L. O’Gorman et al ¹¹⁵ proved that preoperative MRI fused with postoperative CT offers an alternative method for evaluating electrode position, but before this method can be clinically applied, the image registration accuracy must be established. This study quantitatively assessed the accuracy of three different image registration and fusion methods. The mean error along the lateral, anteroposterior, and vertical axes was 0.5, 0.5, and 1 mm, respectively. This study concluded that CT/MRI fusion provides a safe, practical technique for postoperative identification of DBS electrodes. The most accurate registration protocol was that using MSS (Medtronic StealthStation). The results of this study confirmed that a mean accuracy of 1 mm is typically achievable between postoperative stereotactic CT and preoperative stereotactic MRI in a group of patients treated with DBS for movement disorders, establishing that CT/MR image fusion techniques can provide a robust and practical method for postoperative assessment of DBS electrode position.

It is commonly accepted that CT scanning provides a precise geometric localization in axial determinations, after linear distortion correction ¹¹⁶. Satisfactory precision is reached also in the vertical axis if thin slices are obtained. MRI scans are more susceptible to spatial distortion due to a number of factors, including inhomogeneities of the constant magnetic field, nonlinearity of the gradient field, linear scale error, instrument imperfections, magnetic susceptibility artefacts and the effects of local magnetization

^{117,118,119,120,121}. Several authors have suggested that image fusion with CT scans may improve the accuracy of spatial targeting over that achieved using MRI alone ^{122,123,124,125}. CT-MR image fusion is increasingly used for stereotactic DBS electrode placement.

ERROR OF PLACEMENT

The isolated extreme electrode tip, if correctly placed, should ideally have the same stereotactic coordinates that were set by the surgeon on the frame during the surgical procedure. Each stereotactic procedure introduces an error that can be quantified by using modern fusion technologies.

Taking into account that the electrode diameter is 1.27 mm and that the current spreads into the surrounding structures, a less than 1-mm placement error should be considered acceptable. Human error, tissular mechanic impedance, electrode mechanic impedance, frame age and maintenance certainly play a role in determining placement error. To achieve this millimetric precision, a rigid insertion cannula has to be used. In a study by Paolo Ferroli et al ¹¹⁰, postoperative MR images were fused with the pre-operative stereotactic CT. The placement error in the anteroposterior, lateral and vertical planes was calculated.

The anteroposterior mean error $\pm$ SD was 0.61 ± 0.22 mm (range 0.2–0.9 mm). The lateral mean error $\pm$ SD was 0.65 ± 0.27 mm (range 0.2–2.2 mm). The vertical mean error $\pm$ SD was 0.82 ± 0.31 mm (range 0.3–1.6 mm)

The vertical error is found to be slightly higher than the placement error in both the anteroposterior ($p = 0.025$) and the lateral planes ($p = 0.031$). This depends upon the slice thickness. More the slice thickness, more the vertical error of placement. In addition, possible micromovements of the electrode during the bone-fixing manoeuvres should be considered, and use of fluoroscopic control should be mandatory.

ROLE OF THE NEUROLOGIST AFTER SURGERY

The setting of electrical variables after surgery requires that the neurologist develop and maintain the competence to manage this new therapy in combination with drugs. To avoid dyskinesias in parkinsonian patients stimulated in the STN, a slow and progressive increase in voltage is recommended while the levodopa dose is concurrently decreased.⁸⁸ Whatever the targets, electrical parameters are adjusted based on clinical improvement and side effects. One can use a monopolar configuration with the active contact serving as the cathode, and the reference as the case of the stimulator, or a bipolar configuration with the reference as another contact. The latter focuses the effect of stimulation, which can be advantageous in the case of adverse effects or a narrow therapeutic window caused by a misplaced electrode. Majority tend to favor monopolar stimulation that is usually effective with a lower voltage than bipolar stimulation. Frequencies above 100 Hz, typically 130-185 Hz, are mainly effective. Pulse widths of 60-90 μ s, rarely higher, are the most commonly used. Setting the narrowest pulse width minimizes

consumption in comparison with a wider pulse width and a lower voltage for similar effects ¹²⁶ . Increasing the voltage higher than approximately 4.0 V generally means that the suitable target has not been attained. Such voltages usually induce adverse effects, whereas the beneficial effect has already reached a ceiling.

Electrical settings must be determined far from a drug-induced effect (i.e., in the worst off-motor period for PD patients) and checked afterward in the levodopa-induced dyskinesia period. It seems that patients with severe presurgical levodopa-induced dyskinesias are prone to developing STN stimulation-induced dyskinesias in the postsurgical period. Voltage must be increased slowly in such patients, and the progressive increase in the voltage threshold capable of inducing dyskinesias may take months and is facilitated by levodopa arrest ¹²⁷ . A complete stimulation setting includes individually testing each of the four contacts of the quadripolar electrode to determine the threshold voltages for both the beneficial and adverse effects on the disabling symptoms. Similar to what is observed during surgery, the best contact is the one with the lowest threshold for motor benefit and the highest for adverse effects. Refining this electrical setting fully is time-consuming, but it is done only once after surgery, once after the healing process, and generally once at a 3-month follow-up. Over the long term, the same results are usually obtained, and thus a new setting typically focuses only on the smallest possible variations for all types of parameters. Transient improvements often have been observed

continue gentle irrigation until the hemorrhage is cleared while monitoring the patient for neurological status. Any neurological deterioration such as the onset of lethargy or a new focal deficit is cause for stopping the procedure and proceeding immediately to the CT scanner. If the patient cannot protect his or her airway, they should be intubated prior to leaving the operating room. Equipment to perform an emergent craniotomy should be readily available at all times. Unexpected electrical silence not attributable to problems with the electrode itself or its position (such as in the internal capsule) should raise the suspicion of an intraoperative hemorrhage. In addition, deviation of the electrode tip on fluoroscopy after placement not only signals the presence of the development of an intracranial hemorrhage, but also provides some information as to the magnitude of the problem.

POSTOPERATIVE COMPLICATIONS

The real therapeutic value of DBS in advanced PD must take into account the risk of severe adverse effects leading to permanent neurological aftereffects. Intracranial hemorrhage associated with surgery occurred in 2% to 3% of cases^{83, 128}. Risk factors might be age, number of electrode passes⁸³, and history of arterial hypertension.¹²⁹ Perioperative mortality is less than 1% of cases.

Also noteworthy in this regard are complications related to the implant, such as infections, skin erosions, and lead breakage. This led to discontinuation

of treatment in 6.1% of patients in a multicenter study with 4 years of follow-up ¹³⁰. These side effects generally can be managed without permanent morbidity.

The Toronto group systematically reviewed the published literature describing patients with PD treated with bilateral STN stimulation from 38 studies and 34 neurosurgical centers in 13 countries. The outcomes for 471 patients showed a 1% to 2% incidence of severe adverse effects (death or permanent neurological deficits related to intracerebral hemorrhages). Of the patients, 19% had adverse effects related to stimulation that could be reversed by changing stimulation parameters. There was a 9% incidence of adverse effects related to the hardware (infections, lead and pulse generator problems)

¹³¹

In a study by J. Herzog et al.⁹⁶ serious adverse effects of STN-DBS were rare. Relevant side effects necessitating surgical intervention included an intraoperative subdural hematoma without any neurological sequelae in 1 patient and minor intracerebral bleeding at the side of the trajectory of the lead was noted. Transient psychiatric symptoms were the most common therapy-related adverse effects.

Globally, infection rates range from less than 1% to as high as 14% ¹³². Infections of the IPG site tend to present soon after surgery. Infections at the connector may be related to skin erosion and may present at variable times

after implantation. Skin reactions and erosions above the device components are easily diagnosed by inspection of the area, which has to be done routinely by the neurologist at every follow-up. Any patients with suspected abnormalities must be sent to the neurosurgeon. Therapeutic strategies in cases of active infection involve mainly the removal of hardware, or antibiotics alone if there is no erosion, but with a high risk of failure ¹³³. Reimplantation can be performed safely after resolution of infection and a sufficiently long period of antibiotics.

DBS electrode fracture, extension wire failure, consumption, and/or malfunction of the IPG ¹³⁴ cause loss of efficacy for the patient. If the battery has run out, replacement of the IPG will solve the problem. If this is not the case, the impedances through the electrodes must be measured using the nominal setting with a higher tolerable voltage for greater accuracy. X-rays of the system may show a fracture in the DBS electrode or extension lead, or a disconnection ¹³⁵. Replacement of the damaged DBS material is the only treatment for this type of malfunctioning. For a given center, most hardware-related problems frequently occurred in the first patients of a series and were less frequent afterward. This sheds light on the sophisticated nature of the procedure, which requires a lot of expertise for the neurosurgeon to acquire before getting into a routine with DBS surgery.

Other complications are frequent (see the Table) but transient or benign, without aftereffects. The transient confusion observed in some patients may be

related to intracranial contusion or minimal bleeding, but such nonspecific factors as the long duration of brain surgery and the withdrawal of dopaminergic drugs can be implicated. Those patients became easily confused sometimes after changing the regularity of the levodopa intake due to the formal assessment protocol or to the transient levodopa arrest for MRI or surgery. Most patients with STN or GPi stimulation gained weight ¹³⁶. Discomfort may appear about the extension lead, which can pull in the lateral region of the neck or about the stimulator in the subclavicular area. Scars may be unsightly, as can the bump made by the thickness of the cable connector in the parietal region of bald patients with thin scalps. New flat connectors minimize this side effect.

ADVERSE EFFECTS RELATED TO DEEP-BRAIN SURGERY IN MOVEMENT DISORDERS

Relation with the Surgical Stage	Adverse Effects	Mean Rate
1. Stereotactic frame and ventriculography	Seizure, Mental confusion Extracerebral hematoma	About 1% when ventriculography is performed
	Mental confusion	
	Extracerebral hematoma	
2. Electrode implantation	Transient confusion or bradyphrenia	Up to 10% in PD
	Focal cerebral contusion or stroke; may be asymptomatic and only visualized on postoperative MRI	About 5%, half asymptomatic
	Intracerebral bleeding; may be asymptomatic if small	1 to 5% for all bleedings; 2% to 3% with severe permanent aftereffects
	Intracranial extracerebral bleeding	
	Intracerebral abscess	Very rare
	Electrode fracture or failure (one or more of the 4 contacts) or migration	Unknown
	Misplaced lead	Frequently suboptimal; reimplantation to be considered after MRI checking
3. Connection lead and IPG	Superficial infection: aggressive antibiotherapy	1% to 15% for all types of infections
	Deep infection with cutaneous erosion: material removal and further replacement	
	Breaking or failure of extension lead	More frequent in patients with cervical dystonia
	Skin erosion, foreign body reaction, granuloma, seroma, and pain over the pulse generator	More frequent with Kinetra IPG
	IPG repositioning, pain over the extension lead or IPG region	All hardware problems in about 10% of cases
	IPG malfunction	Rare, rate unknown
4. Others	Transient general state complications, including aspiration pneumonia, pulmonary or urinary infection, thrombophlebitis, pulmonary embolism, etc.	5% of cases, mainly in PD patients; age and severity of akinesia are risk factors
5. Stimulation-induced	Eyelid-opening apraxia	15% in Parkinson's disease patients with STN stimulation
	Dysarthria, dysphagia	
	Motor contraction, paresthesias	20% on the whole, mostly reversible
	Sweating, flushes	
	Imbalance, dyskinesias	
	Psychiatric symptoms	

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In a data from Kenney et al ¹³⁷ adverse effects noted were intraoperative Vasovagal response (2.5%), Syncope (1.2), Severe cough 3(0.9), IVH (0.6), ICH (0.6), Arrhythmia (junctional rhythm) (0.3), Confusion (0.3), Extreme anxiety (0.3), Headache (15.0), Confusion (5.0), Hallucination (2.8), Nausea/vomiting (1.6), Seizure (1.2), Dysarthria (0.9), Dyskinesia (0.6), Hypertension (0.6), Paranoia (0.6), Paresthesia (0.6), Urinary retention (0.6), Deep vein thrombosis (0.3), Depression (0.3), Dizziness (0.3) Insomnia (0.3), Pulmonary edema (0.3), SDH (evacuated) (0.3). Long-term (2 wk) adverse effects noted were Infection (4.4), Cognitive dysfunction (4.0), Dysarthria (4.0), Worsening gait (3.8), Agitation (1.6), Paresthesia (1.2), Depression (0.9), Headache (0.6). Psychogenic tremor (0.6), Urinary incontinence (0.6), Blepharospasm (0.3), Emotional lability (0.3), Insomnia (0.3) Metallic taste (0.3), Suicide (0.3).

Optimal surgical positioning of the stimulating electrode helps to reduce the risk of stimulation-induced side effects that result mostly from unintended costimulation of adjacent fiber tracts or nuclei. Stimulation-induced side effects are fully reversible when stimulation is stopped and can be improved in most cases by changing stimulation parameters or electrode configuration. They include paresthesias, dysarthria, motor contraction, eye deviation, gaze deviation, nausea, dizziness, flushing, discontinuation of the effect of levodopa with worsening of akinesia, and rarely mood or behavior alterations.

Although adverse effects occur frequently, those inducing permanent neurological impairment are relatively rare, in the region of 3%. Therefore, in the face of clinically valuable improvement in motor function, the benefit-to-risk ratio of the DBS procedure seems favorable, at least in severely disabled patients. A careful selection of patient candidates for surgery should help maintain a relatively low level of morbidity. A skilled multidisciplinary team is needed to ensure the quality of patient selection, operative technique, intraoperative monitoring, and postoperative management.

RESULTS OF SUBTHALAMIC NUCLEUS DEEP-BRAIN STIMULATION – OUTCOME

Bilateral subthalamic nucleus stimulation has been studied in idiopathic, levodopa-sensitive young (mostly < 70 years) PD patients suffering from motor complications of levodopa therapy. In such patients, almost all studies report postoperative improvement in off-period motor scores between 40% and 70% ^{138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158}.

In a study by J. Herzog et al. ¹⁴¹ at 6 months follow-up, the UPDRS III total score was reduced by 50.9% in comparison to the preoperative baseline (preoperative, 44.2 ± 13.9 ; postoperative, 21.7 ± 11.5). At 12 months follow-up, the UPDRS III total score was reduced by 57.5% .

Russmann et al ¹⁵⁹ have separately analyzed outcome depending on age. In 52 consecutive patients, improvement in UPDRS motor scores was 62% in

those who were younger than 60 years ($n = 15$), 37% in the group of patients ($n = 24$) ages 60 to 70 years, and only 22% in those more than 70 years (mean 74 ± 3 ; $n = 13$). In a recent review by Hamani et al¹³¹, the average improvement 12 months after surgery was found to be 56% . After 12 months of subthalamic nucleus stimulation, when compared with preoperative off-medication subscores, the mean improvement was 81% in tremor, 63% in rigidity, 52% in bradykinesia, 64% in gait, and 69% in postural instability . Contrary to other parkinsonian signs, speech is generally not improved with STN stimulation^{33,130,142} .

Some groups have reported a smaller improvement in UPDRS motor scores Ford et al¹⁶⁰ believe that their more modest results represent a more realistic estimate of the effect of DBS on PD based on the fact that they used a double-blinded evaluation of the motor UPDRS as their main outcome criterion. However, their data differ greatly from the vast majority of published outcomes including double-blind, crossover evaluations^{161,162} not only in the double-blind evaluation but also in nonblinded assessment of several secondary outcome measures, including activities of daily living (no benefit) and postoperative decrease in dopaminergic treatment (30%).

On-period motor signs are not improved with subthalamic stimulation, provided care is taken to use an individually adapted suprathereshold dose of levodopa to carry out the levodopa test^{71,142} .

Many authors, however, report a 30% to 40% improvement in on-period motor scores ¹⁴³ related to improvement in tremor and rigidity ¹³⁰. This difference in outcome measurements reflects differences in evaluation techniques that are likely to be explained by the fact that not all authors use supratherapeutic doses of levodopa as a levodopa challenge, but rather they evaluate while the patient is receiving optimal medication therapy, including levodopa, dopamine agonists, and other antiparkinsonian medication ¹⁴³.

Activities of daily living in off-drug conditions, as measured by UPDRS Part II, improve to the same extent as improvement in motor symptoms ¹⁶¹. Although on-period dyskinesias improve, activities of daily living in on-drug conditions remain unchanged ⁷¹ indicating that dyskinesias on average do not have a major impact on activities of daily living, in contrast to parkinsonism.

Data concerning cognitive or behavioral deterioration must be viewed with caution as most studies suffer from small sample sizes and generally do not include PD control groups ^{163,164}. In this context, an article analyzing postoperative behavioral side effects and preoperative history of behavioral side effects found that those patients displaying behavioral abnormalities after surgery generally had a history of exactly the same behavioral abnormalities before surgery, thus illustrating that not every reported abnormal behavior should be seen as directly related to stimulation and even less as a specific side effect of a specific target ¹⁰¹. Analysis of long-term follow-up after STN surgery shows that immediately after surgery there is a high prevalence of

confusion and behavioral side effects, but in the long term, cognitive and psychiatric side effects are relatively rare ⁷¹ The side effects in the first weeks or months are multifactorial. They can be related to surgery or to changes in medication and stimulation, and sometimes they are reactions to a life event. A side effect occurring several months or years after surgery can be related either to treatment or to progression of the disease, and sometimes it may be completely independent of PD and its treatment. Apathy is a frequent finding in PD patients on chronic subthalamic stimulation ^{71, 99}.

Postoperative transient hypomania is a frequent finding ^{71,99} and some cases of full-blown mania also have been reported ^{96,165}. Hypomania is a specific effect of stimulation of the limbic STN. In the postoperative period, the interaction among the short-term psychotropic effects of dopaminergic treatment ¹⁶⁶; the ongoing long-term effects of dopaminergic treatment in the first weeks after reduction of treatment ¹⁶⁷ and the transient lesionlike effects of surgery related to an edema surrounding the electrode contribute to the psychotropic effects of subthalamic stimulation. The publication of acute stimulation-induced depression ¹⁶⁸ using an electrode close to the STN, as well as reports on suicides after STN surgery ^{101,105,142} have raised much concern. Preoperative depression and a history of repeat surgery were found to be risk factors for postoperative suicide, also pointing to selection bias ¹⁰⁵. Depression is a frequent finding in the patient population requesting surgery ^{95,101} and patients with suicidal ideation are at risk, require optimal antidepressant

treatment, and need a close psychiatric follow-up. L-dopa withdrawal and reactive depression also may play a role in patients at risk. The majority of the observed neuropsychiatric symptoms are considered to be transient, treatable, and potentially preventable ¹⁶³.

Quality of life is an interesting outcome measure as it takes into account not only the motor benefits but also changes in pain, sleep, mood, autonomy, and social adaptation, as well as the impact of side effects, whether cognitive, motor, or behavioral. One study has used a generic measure of health-related quality of life showing improvements in physical and psychosocial dimensions. The most improved aspects included body care, movement, sleep and rest, ambulation, social interactions, and recreation and pastimes ¹⁶⁹ Several studies focused on disease-specific aspects of health-related quality of life ^{170,171,172,173,174,175} and consistently showed greater improvements in subscores of mobility, activities of daily living, stigma, emotional well-being, and bodily discomfort, whereas social support, cognition, and communication were less improved. ¹⁷⁶ The quality of life of caregivers also was improved ^{177,141,178}.

Improvement of motor symptoms and dyskinesias, and a decrease in dopaminergic medication, are largely sustained in the long term ^{130,160}. Mild worsening of akinesia, mainly of such axial features as speech, postural reflexes, and freezing, occurred over time ⁷¹. There also was progressive worsening of apathy and frontal dysexecutive syndrome, and some patients

developed dementia. There is no indication of tolerance as effects are stable over 5 years with no increase in stimulation parameters after the first year ⁷¹. Progression of symptoms over time closely resembles the natural history of PD on medical treatment but without the motor complications ^{179,180} and these changes are therefore believed to represent progression of the disease rather than side effects of stimulation. This is compatible with a longitudinal positron emission tomography (PET) study showing continuous decline of dopaminergic function in patients with advanced PD under clinically effective bilateral STN stimulation, with rates of progression that are within the range of previous studies in nonstimulated patients ¹⁸¹. According to evidence-based criteria, subthalamic nucleus stimulation is considered as efficacious and clinically useful as an adjunct to levodopa ¹⁸².

AIMS AND OBJECTIVES

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1. To compare functional outcome of different methods for targeting of STN .
2. To analyze the accuracy of deep brain stimulation (DBS) electrode placement with the use of image fusion technologies.

MATERIALS AND METHODS

MATERIALS AND METHODS

Retrospective analysis of 20 consecutive patients with idiopathic Parkinson's disease treated with STN deep brain stimulation at SCTIMST between October 2006 to July 2009 was carried out.

INCLUSION CRITERIA

1. Significant impairment of ADLs [Activities of Daily Life] and quality of life due to motor fluctuations and levodopa-induced dyskinesiae despite maximal drug therapy
2. Physically healthy with potentially a long life expectancy after surgical treatment
3. Physical and mental stamina to provide feedback during a lengthy operation
4. Patients must have good family and strong emotional support pre- and postoperatively.

EXCLUSION CRITERIA

1. Poor levodopa-response with significant on-period disability
2. Significant cognitive impairment

3. Uncontrolled cardiac, renal, hepatic, pulmonary disease, cancer or hypertension
4. Significant psychiatric illness including anxiety, mood disorders, and severe depression, which could worsen post-operatively
5. Marked cerebral atrophy or extensive white matter T2 signal changes, which could increase the risk for hemorrhage
6. Atypical parkinsonian syndromes

All patients underwent detailed neurologic evaluation by a senior movement disorder specialist and were evaluated with stringent criteria for selection of candidates for STN DBS.

Patients were divided into three different groups according to surgical methodology used for targeting STN.

GROUP 1

This group included 7 patients.

The surgical protocol used was as follows:

1. Preoperative stereotactic MRI. Leksell stereotactic frame was used in all cases. SIEMENS 1.5T and GE 1.5T (earlier part of the study) scanners were used.

2. Localisation of STN using direct method (direct visualisation of STN on MRI console and obtaining the stereotactic coordinates manually) and indirect method (based on fixed distance on the STN from the midpoint of AC-PC line, laterality 12mm, 2mm anterior to mid AC-PC point and 4mm inferior to AC-PC line). The MRI DICOM images were loaded on the Elekta Surgiplanner system which derived the AC-PC coordinates . Final coordinates were taken as average of these 2 methods based on the hypothesis that the averaging eliminated the MRI distortion induced error of direct calculation and the error of indirect AC-PC based calculation which is derived from cadaver based atlases(does not address patient anatomy directly).
3. Planning the safe trajectory to avoid cortical veins, sulci, ventricles and enhancing vessels in the brain.
4. Intraoperative Microelectrode recording (MER) was performed using 5 electrodes (MEDTRONIC) mounted on the BENGUN (anterior, lateral,medial,posterior and central electrode positions)for stereotactic submillimetric insertion into the brain with help of the microdrive mounted on the BENGUN .The electrodes recorded the neural activity from the thalamus,STN and SNR thereby giving the dimensions of the STN electrophysiologically . This technique was used in all the cases uniformly.

5. Selection of tract based on best clinical response (macro electrode stimulation was done in each track methodically using incremental current at high and low frequency to check benefit and side effects)
6. Implantation of electrodes at desired target (Elelectrophysiological STN) after adjusting depth and laterality, using C-arm guidance.
7. Implantation of neurostimulator under General Anaesthesia.
8. Postoperative nonstereotactic MRI

Accuracy of electrode placement between preoperative target and postoperative MRI artefact was subjectively (visually) confirmed.

GROUP 2

This group included 7 patients. The surgical protocol was as follows:

1. Preoperative stereotactic MRI (T2 Axial-for localizing STN, T2 Coronal for localising STN, PostGadolinium Axial 3D FLASH for avoiding blood vessels and sulci and for obtaining a trajectory along the long axis of STN) on the day of surgery.
2. Calculation of STN coordinates by direct and indirect method (AC-PC based)
3. Transferring images to Medtronic stealthstation (neuronavigation DBS protocol software “Framelink”) followed by merging all sequences (T2\

Axial, T2 Coronal , Postgadolinium Axial) with each other to achieve accurate merging

4. Localisation of STN using direct visualisation on MRI and calculation of framelink coordinates
5. Final coordinates decided by best among the above methods or average of all methods, whichever matches best with STN (By match it is meant that the proposed trajectory of 5 electrodes should transfix the STN with the central track traversing the centre of the nucleus)
6. Planning the safe trajectory on stealthstation using framelink coordinates to avoid sulci and ventricles.
7. Intraoperative Microelectrode recording (5 track) and localisation of electrophysiological STN
8. Selection of best tract based on best clinical response (upon macro electrode stimulation) and minimal side effects
9. Implantation of electrodes at desired electrophysiological target.
10. Implantation of neurostimulator under GA.
9. Postoperative nonstereotactic MRI

Accuracy of electrode placement between preoperative target and postoperative MRI was subjectively (visually) confirmed in 3 patients. Preop

stereotactic MRI was fused with postoperative nonstereotactic MRI on Stealthstation machine and accuracy of electrode placement was calculated in last 3 patients, based on position of postoperative electrode artefact in relation to preoperatively localised STN.

GROUP 3

This group included 6 patients. The surgical protocol was as follows:

1. Preoperative nonstereotactic MRI. This study is loaded on “framelink” and AC-PC based coordinates of STN are obtained along with safe trajectory to STN. These coordinates cannot be transcribed onto the stereotactic frame. This study is done a few days prior to the day of surgery. During this study patient takes all the medication and thus remains in the “ON” state thereby avoiding “OFF” state discomfort. The surgeon gets adequate time to do the planning in relaxed conditions
2. Stereotactic CT on day of surgery (with frame) . Medication is omitted 1 night prior to the day of surgery as Levodopa suppresses MER recording during surgery. Since the MRI study is already over and planning is complete, the time patient is in “OFF” state is minimized thereby maximizing comfort levels and ability to cooperate during the procedure. In the “OFF” state patient becomes bradykinetic, rigid with hypophonia and “low energy” levels. When the second side surgery is

being performed the patient is hardly able to respond to requests during clinical assesment of benefits and side-effects of stimulation.

3. Transferring CT images to “Framelink” and merger of stereotactic CT with nonstereotactic MRI. The CT scan scan study becomes the reference study (registration series). Since CT scan is based on X-rays it is not associated with distortion which occurs in MRI study. This theoretically increases the accuracy of electrode placement
4. Fusion of stereotactic CT with nonstereotactic MRI on framelink now give stereotactic coordinates which can be transcribed on to the stereotactic frame
5. Intraoperative Micro electrode recording (5 track) and localisation of electrophysiological STN
6. Selection of tract based on best clinical response (upon macro electrode stimulation) and minimal side effects
7. Implantation of electrodes at desired electrophysiological target. Fibrin glue was used in few patients to fix burr hole cap .
8. Implantation of neurostimulator under GA.
9. Postoperative nonstereotactic CT
10. Fusion of preoperative nonstereotactic MRI /stereotactic CT with postoperative nonstereotactic CT to calculate accuracy of electrode

placement . The stereotactic coordinates of the actual electrode tip can be matched with stereotactic coordinates of STN to assess the accuracy of placement. Also the stereotactic coordinates of the active contact of the electrode can be obtained and the position of the active contact in relation to STN calculated (for e.g. the active contact can be in the white matter above STN nucleus or it can be in the dorsal STN).

The MRI and CT protocol used in all 20 patients were as follows:

DBS – MRI PROTOCOL

Preoperative Nonstereotactic MRI

Name Of Machine : SIEMENS MAGNETOM AVANTRO TIM

Field Of View (FOV) : 280 mm

Voxel: 1.1 X 1.1 X 3 mm

Matrix: 256 X 256 square matrix

Total 3 Sequences : non interleaved with 0 interslice gap (2 T2-FSE AND 1 FLASH 3D CONTRAST)

T2 FSE 2D(FAST SPIN ECHO) is also called as T2 TSE-2D (TURBO SPIN ECHO)

Sequence 1. Axial Sequence T2FSE 2D

Sequence 2. Coronal Sequence T2 FSE 2D

Passing through mid AC-PC and 2 mm anterior to mid AC-PC

Specifications common for sequence 1 & 2

Slice thickness: 3 mm.

TR: 5010 (Repetition Time)

TE: 85 (ECHO Time)

Signal excitation : 3

Bandwidth: 156 Hz / PIXEL

Scan time : 5.47 seconds

Sequence 3. FLASH 3-D also called 3D-GRE Contrast

Specifications For Sequence 3

Slice Thickness: 2 mm.

TR: 11 (Repetition Time)

TE: 4.94 (ECHO Time)

Signal Excitation : 1

Bandwidth: 140 Hz / Pixel

Scan Time : 6.21 seconds

STEREOTACTIC CT PROTOCOL

GE HIGH SPEED SPIRAL CT

Single Slice

3mm Thickness

FOV: 280 mm

512 x 512 matrix(Square matrix)

Antiparkinsonian and antitremor medications were withheld overnight before surgery so as to maximize tremor and off-period parkinsonism to allow optimal intraoperative assessment of the benefits of stimulation.

Intraoperatively Microelectrode recording and macrostimulation were used to determine the best possible location for the DBS electrode, optimal benefit and a large therapeutic window between beneficial and adverse effects. With macrostimulation, the expert neurologist team assessed the threshold for adverse and beneficial effects (such as improvement in tremor, bradykinesia, and rigidity). Adverse effects due to current spread to adjacent structures were evaluated and include paresthesias, tonic motor contraction, eye deviation, tongue deviation, dysarthria, photopsias, and vegetative or affective symptoms (sensations of heat or sweating, depression, or euphoria). Final electrode position was determined by best clinical response and least side effects. The radiological target was adjusted according to desired electrophysiological location. 5 channel Ben's gun was used to mount and advance the electrodes.

Dexmedetomidine infusion was used for last 4 patients of group 3 for sedation and it did not interfere with MER.

DBS ELECTRODE USED

The DBS electrode (Medtronic, Minneapolis, MN) consisted of 4 contacts, with each contact 1.5 mm in length and separated by 0.5 mm (**Model 3389**).

PLACEMENT OF IMPLANTABLE PULSE GENERATOR (IPG)

The hardware was secured to the skull with a plastic cap fitting into the burrhole. Fibrin glue was used in few patients for fixing burr hole cap. The IPG was implanted the same day as the DBS electrode .The IPG was implanted under general anesthesia in the left subclavicular area. Extension cables (Extension Kit 7495) connected the IPG to the DBS electrode and run from the skull, behind the ear and over the mastoid process, and then subcutaneously through the neck.

IMPLANTABLE PULSE GENERATOR

Kinetra model was used for all patients . The Kinetra is a dual channel IPG and comes with the Access Therapy Controller, which allows the patient to turn the stimulator off and on as well as modify the stimulation amplitude within parameters specified by the physician. Stimulation settings are adjusted by means of a programmer (N-Vision Programmer Model 8840, Software Application Card 8870; or Console Programmer Model 7432, MemoryMod HF Software Cartridge Model 7458) placed on the skin overlying the IPG. The following stimulation parameters were adjustable: frequency (0–185 Hz), pulse width (60–450 microseconds), voltage (0 –10.5 V), and stimulating contacts (monopolar or bipolar stimulation).

PROGRAMMING

For all the patients , programming of the neurostimulator was done in immediate postoperative period and doses of L-Dopa were reduced subsequently.

A few DBS programming sessions were usually necessary to optimize the stimulation settings, although the actual number of sessions required were variable for individual patients.

ASSESSMENT OF UPDRS (Unified Parkinson's Disease Rating Scale)

Preoperatively, motor assessment was performed in the off-state after 12 hours withdrawal of antiparkinsonian medication (*offMed*). According to their pharmacological half-life, other dopamine agonists were discontinued 24 to 72 hours before the levodopa test. Response to levodopa (on state) was evaluated after taking the 1.5-fold of the usual morning levodopa equivalent dose. Patients were under permanent observation of the examiner. The Unified Parkinson's Disease Rating Scale (UPDRS) score was assessed when the patient achieved their best on-state (*onMed*), usually 1 hour after taking the medication.

1 year UPDRS scores (motor UPDRS or UPDRS -III) were calculated for all patients in 'drug on battery off' as well as double off (drug off battery off) .

The scores which were compared for statistical analysis were **preoperative (drug off)** and **postoperative (battery on drug off)** score.

The mean and median UPDRS scores were calculated for each group . The reduction in postoperative UPDRS score was calculated as percentage for each group.

Percentage change was calculated as: $[(\text{Preoperative} - \text{postoperative}) / \text{Preoperative}] \times 100$.

The percentage of improvement in motor UPDRS score (UPDRS-III) was calculated for all 3 groups and then compared with each other by statistical methods (ANOVA), to find out any significant difference between outcomes of the three groups.

ASSESSMENT OF ACCURACY OF ELECTRODE PLACEMENT

STN coordinates of the electrophysiological STN were calculated depending upon track and depth chosen (Electrophysiological STN) [TX,TY,TZ for right side and Tx,Ty,Tz for left side]

These coordinates were compared with preoperative coordinates of best visualised STN on MRI (Radiological STN). [X,Y,Z for right side and x,y,z for left side]

Fusion of preoperative nonstereotactic MRI /stereotactic CT with postoperative nonstereotactic MRI was done for last 3 patients in group 2.

Similarly for all 6 patients of group 3, preoperative nonstereotactic MRI/stereotactic CT was fused with postoperative CT.

The center of the postoperative electrode artefact was chosen as the point for which coordinates were calculated. [PX,PY,PZ for right side and Px,Py,Pz for left side].

Then we calculated the difference in the coordinates of electrophysiological STN (point where we intended to implant the electrode) and postoperative electrode location(point where we have actually implanted).

This gave the mean error of placement in all three axes.

RESULTS

RESULTS

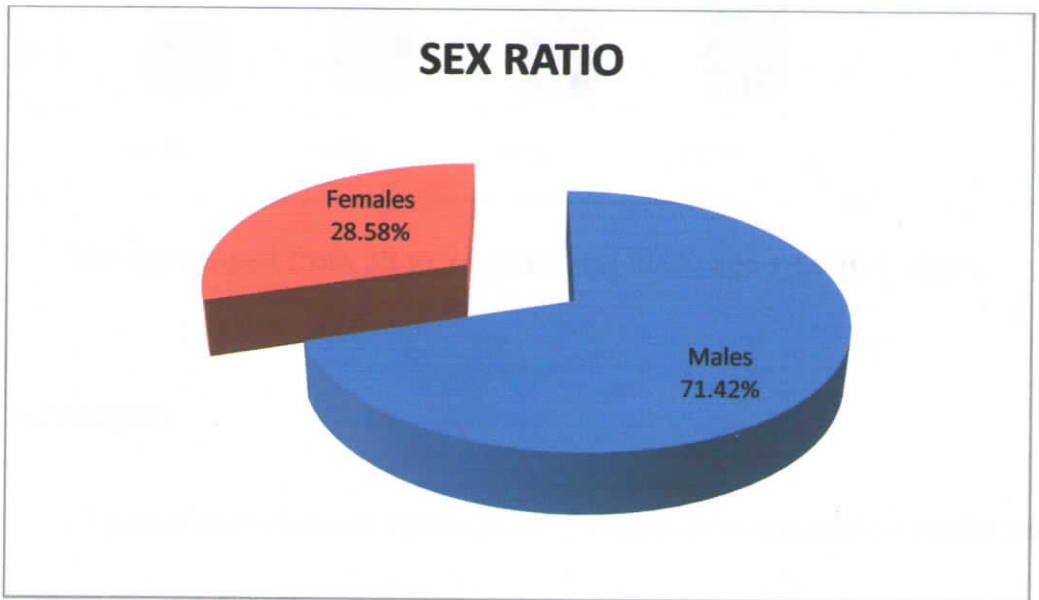
Total of 20 patients underwent bilateral STN deep brain stimulation from October 2006 to July 2009 (consecutive cases with 1 year follow up).

N=20

DEMOGRAPHICS

1. SEX RATIO:

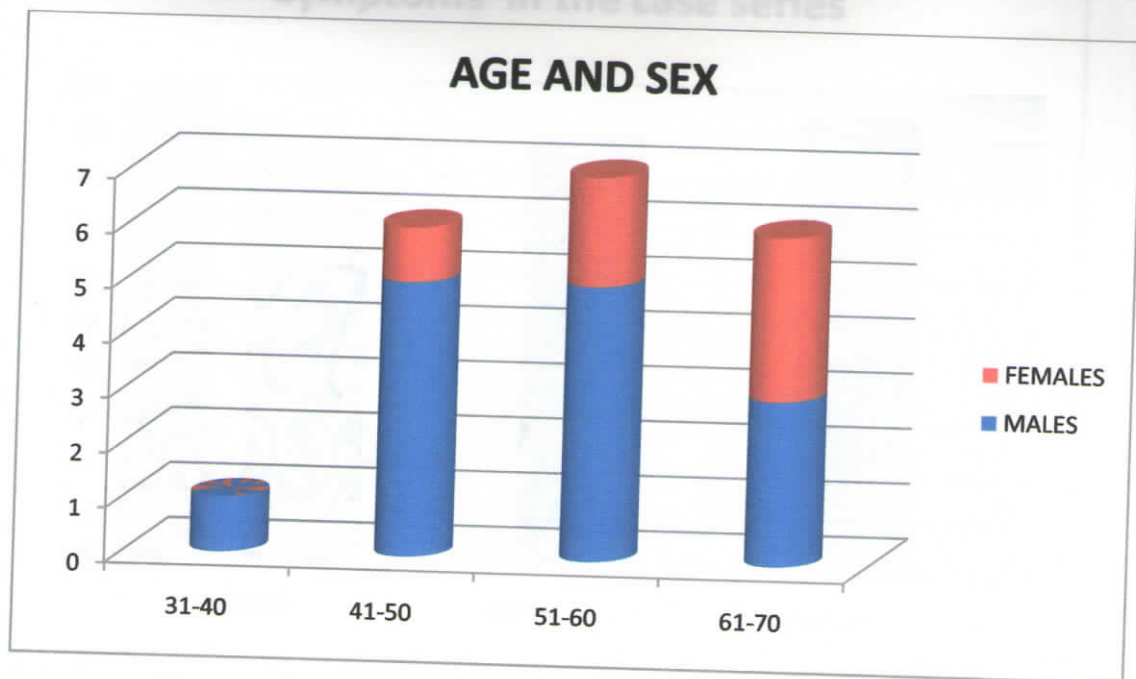
Male : female ratio was 14: 6.



71.42 % patients were males and 28.58% patients were females.

2. AGE :

Symptoms in the case series



The age ranged from 39 to 75 years and mean age was 56.1 years.

3. STAGING

17 patients underwent bilateral STN electrode implantation in the same procedure (single stage).

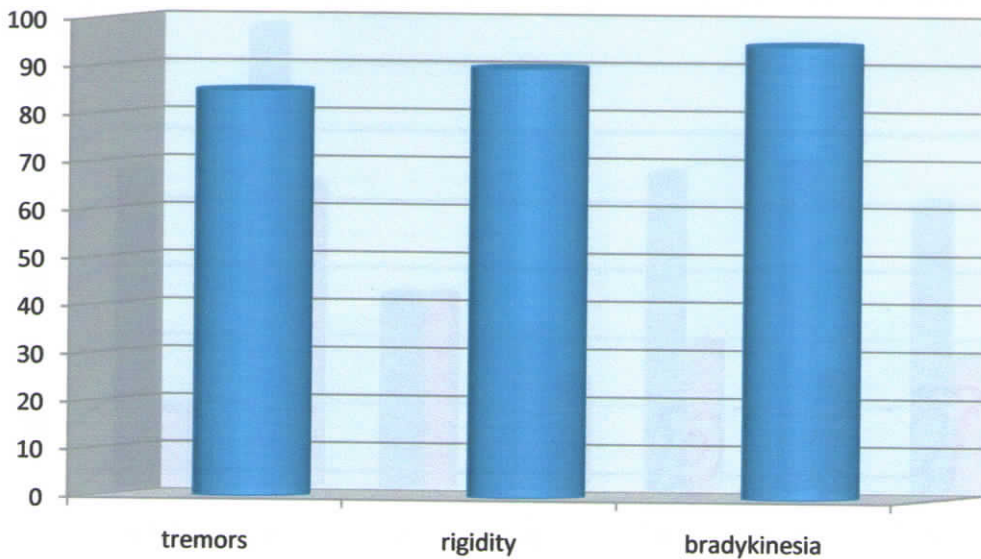
3 patients underwent double stage procedure (2 due to seizure after first electrode implantation).

Mean preoperative symptom duration was 11.95 years.

SYMPTOMS

85 % patients had tremors while 90 % patients had rigidity and 95 % patients had bradykinesia.

Symptoms in the case series



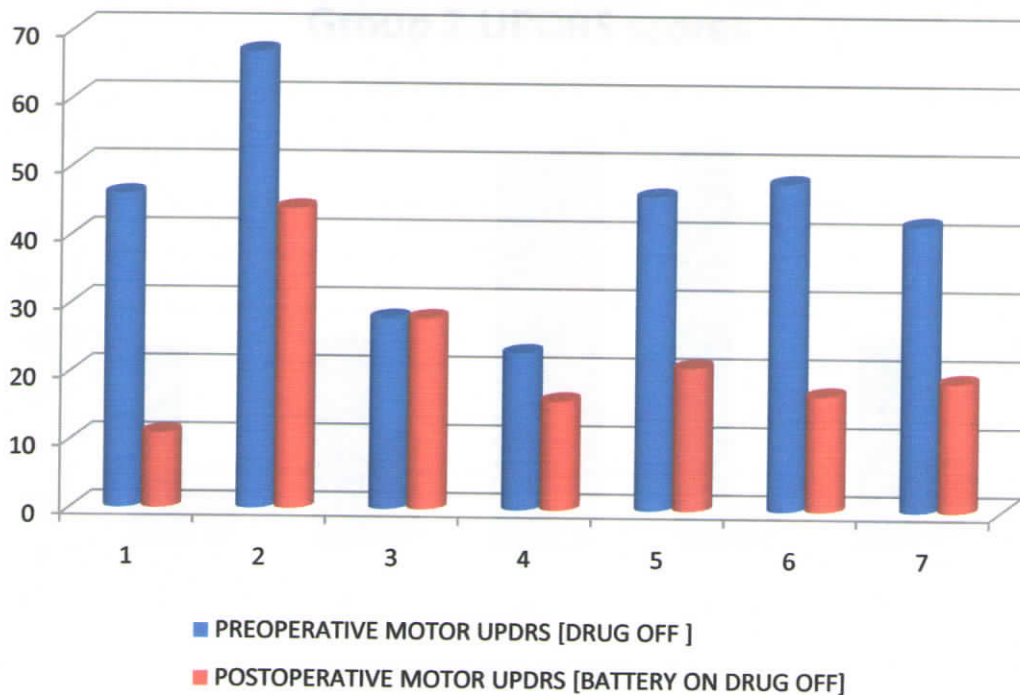
All patients had levodopa [L-Dopa] responsiveness and all of them had L-dopa induced dyskinesiae and motor fluctuations.

OUTCOME OF THREE GROUPS COMPARISON OF PREOPERATIVE AND POSTOPERATIVE MOTOR UPDRS

GROUP 1

GROUP 1	PREOPERATIVE MOTOR UPDRS [DRUG OFF]	POSTOPERATIVE MOTOR UPDRS [BATTERY ON DRUG OFF]
1	46	11
2	67	44
3	28	28
4	23	16
5	46	21
6	48	17
7	42	19

Group 1 UPDRS scores

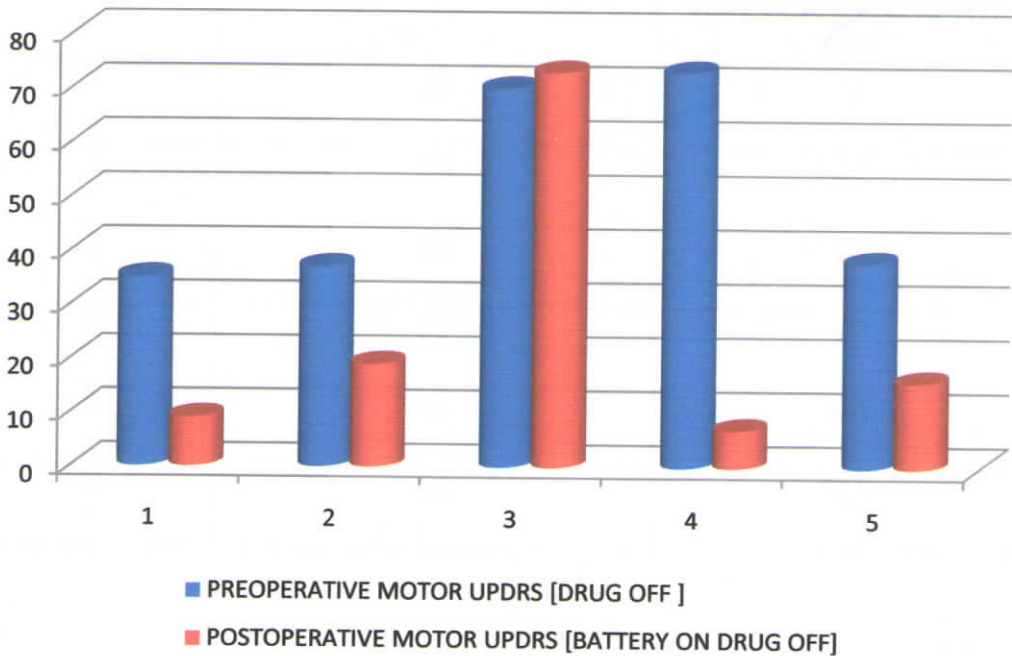


GROUP 2

GROUP 2	PREOPERATIVE MOTOR UPDRS [DRUG OFF]	POSTOPERATIVE MOTOR UPDRS [BATTERY ON DRUG OFF]
1	35	9
2	37	19
3	70	73
4	73	7
5	38	16
6	52	NA
7	35	NA

NA= Not Available

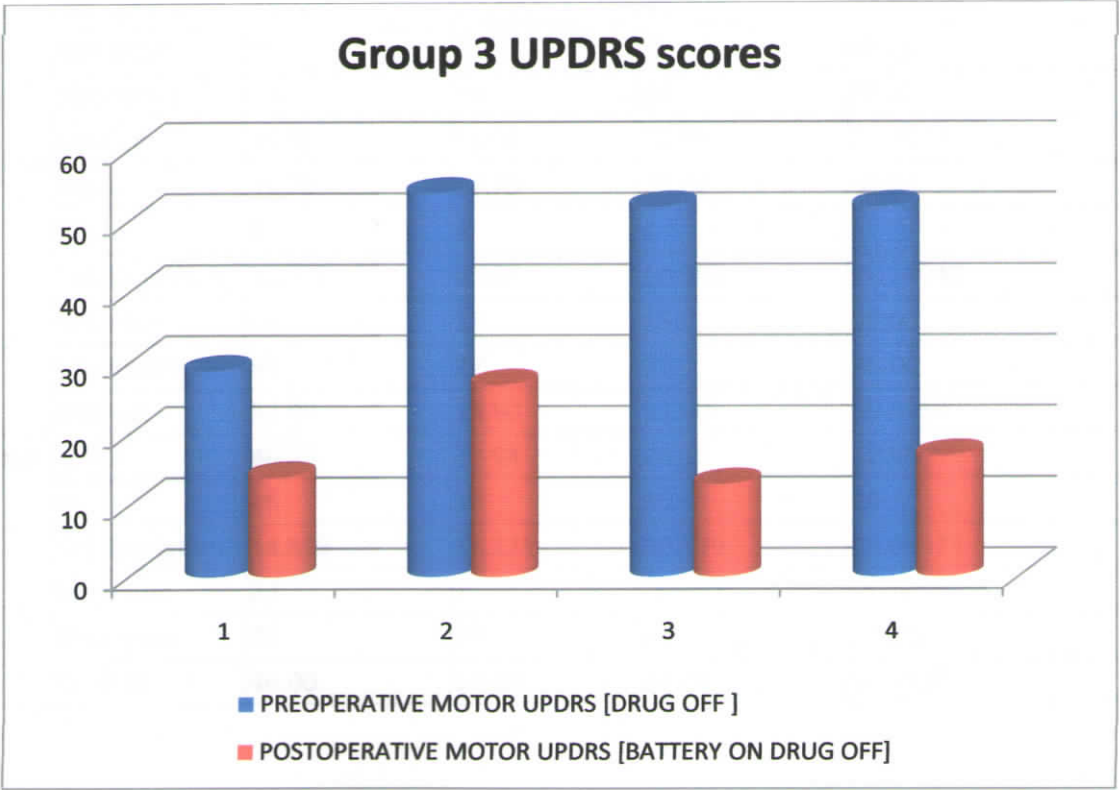
Group 2 UPDRS scores



No. 6 patient had postoperative intracerebral hematoma and electrode implants were removed. He was discharged in a vegetative state and has not come for follow up since then. Hence no postoperative score is available.

No. 7 patient did not turn up for follow up.

GROUP 3	PREOPERATIVE MOTOR UPDRS DRUG OFF	POSTOPERATIVE MOTOR UPDRS BATTERY ON DRUG OFF
1	29	14
2	54	27
3	52	13
4	52	17
5	46	NA
6	66	NA



No. 5 patient expired due to unrelated cause and last patient is still due for follow up.

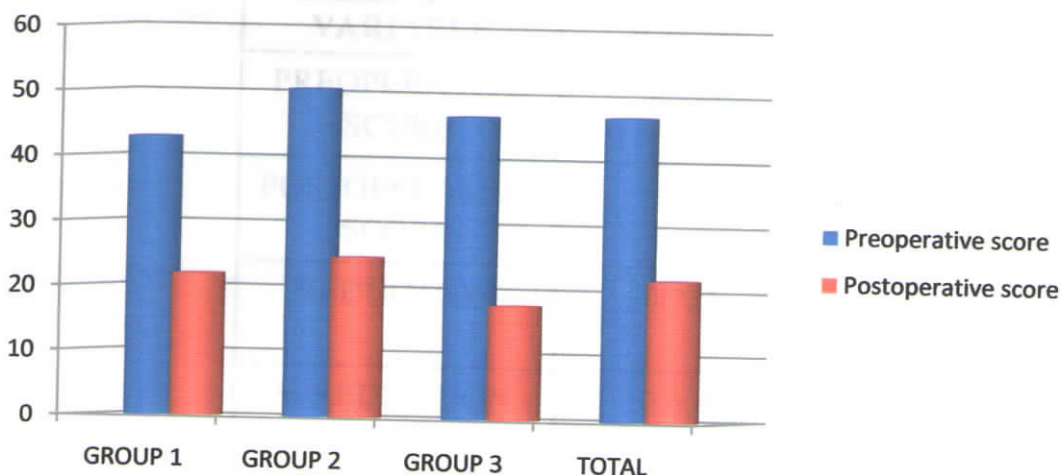
The mean and median UPDRS scores were calculated for each group and are given in table no. 1 .

The reduction in postoperative UPDRS score was calculated as percentage for each group.

Percentage change was calculated as: $[(\text{Preoperative score} - \text{postoperative score}) / \text{Preoperative score}] \times 100$.

GROUP		Preop Score	Postop Score	Reduction	%Reduction
1	Mean	42.86	22.29	20.57	47.99
	N	7	7	7	7
	Std. Deviation	14.404	10.889	12.621	25.44138
	Minimum	23	11	0	00
	Maximum	67	44	35	76.09
	Median	46.00	19.00	23.00	54.3478
2	Mean	50.60	24.80	25.80	50.99
	N	5	5	5	5
	Std. Deviation	19.139	27.390	25.104	35.97375
	Minimum	35	7	-3	-4.29
	Maximum	73	73	66	90.41
	Median	38.00	16.00	22.00	57.8947
3	Mean	46.75	17.75	29.00	62.03
	N	4	4	4	4
	Std. Deviation	11.871	6.397	10.583	12.14946
	Minimum	29	13	15	50.00
	Maximum	54	27	39	75.00
	Median	52.00	15.50	31.00	59.5159
Total	Mean	46.25	21.94	24.31	52.56
	N	16	16	16	16
	Std. Deviation	14.853	16.221	16.349	26.05623
	Minimum	23	7	-3	-4.29
	Maximum	73	73	66	90.41
	Median	46.00	17.00	24.00	54.5549

Reduction in postoperative UPDRS score



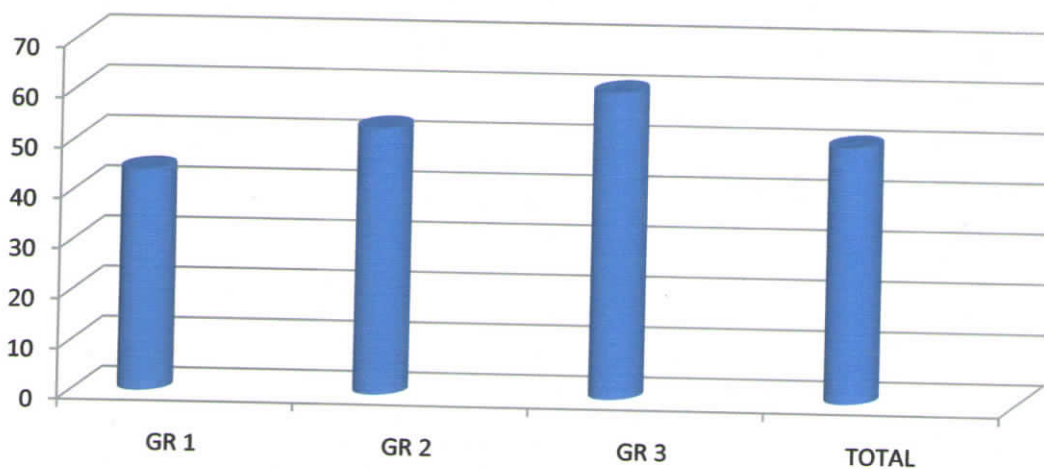
The percentage reduction in group 1 was 47.99%, group 2 was 50.99% , group 3 was 62.03 % .

Overall mean preoperative score was 46.25 ± 14.86 .

Mean postoperative score was 21.94 ± 16.22 . The mean reduction in score was 24.31 ± 16.34 .

The percentage reduction was 52.56%.

Percentage reduction in each group following DBS



ANALYSIS OF VARIANCE FOR PERCENTAGE REDUCTION [ANOVA]

VARIABLE	P Value
PREOPERATIVE SCORE	0.701
POSTOPERATIVE SCORE	0.829
REDUCTION	0.721
% REDUCTION	0.638

P value was calculated for reduction in postoperative UPDRS score using ANOVA(comparison of three groups). It was not found to be significant.

RADIOLOGICAL STN

In our study of 18 STN implantation, in 9 patients , AC-PC based coordinates of center of STN determined by MRI were

Lateral : 10.56

AP : 2.26

Vertical : 4.76.

DIFFERENCE BETWEEN RADIOLOGICAL AND ELECTROPHYSIOLOGICAL STN

In 9 patients we calculated difference between radiological best visualised STN coordinates [x left side and X for right side] and electrophysiological STN (depending upon tract and depth chosen based on intraoperative MER)[TX for right side and Tx for left side]

Patient No.	X-TX	Y-TY	Z-TZ	x-Tx	y-Ty	z-Tz
1	-1.3	1.8	-3.9	3.9	4.1	-7.9
2	-0.7	1	-1.5	3.5	2.5	-4.9
3	1.6	1.8	-2.3	0.9	-0.6	-2.1
4	-1.4	1.5	-2	-1	1.6	-2.3
5	-1.1	1.5	-2.5	0.8	1.4	-2.6
6	0.1	-1.5	-0.8	0	2.7	-0.7
7	1.4	1	-1.6	0.5	0.9	-1.8
8	-0.9	-1.2	-1.6	-2	0	0
9	-0.9	1	-1.7	1.4	3.7	-3.6

The average difference between radiological and electrophysiological STN was

RIGHT SIDE

X=1.04 mm

Y=1.36 mm

Z=1.98 mm

LEFT SIDE

x=1.55

y=1.94

z=2.87

ACCURACY OF ELECTRODE PLACEMENT MEASURED BY FUSING PREOPERATIVE MRI WITH POSTOPERATIVE CT /MRI

In 3 patients preop MRI was fused with postoperative MRI.(Group 2)

In 6 patients preop MRI was fused with postoperative CT. (Group 3)

We calculated difference between tract coordinates (TX for right side and Tx for left side)and final postoperative electrode artefact coordinates. (Px for left side and PX for right side)

Pt.	PX-TX	PY-TY	PZ-TZ	Px-Tx	Py-Ty	Pz-Tz
1	-2.8	0.7	-1.6	-1.1	0	0
2	-0.1	0.7	-2.2	0	0	0
3	-1.6	1.4	-1	1.4	0.2	-1.4
4	1.8	-0.1	-0.9	-0.6	0	2.6
5	0	3.1	-1	0	1.6	0.9
6	0	0	0	1.7	0.1	2.4
7	-0.4	2	-3.2	0	0	0
8	-0.4	-0.2	-4.8	1.7	0.3	-2.4
9	NA	NA	NA	0.7	0.4	-1.6

AVERAGE ERROR OF PLACEMENT

In 1 patient postoperative imaging was not available for right side as patient was staged and no postoperative images were available for fusion.

RIGHT SIDE (total 8 STNs)

X = 0.89 mm

Y = 1.02 mm

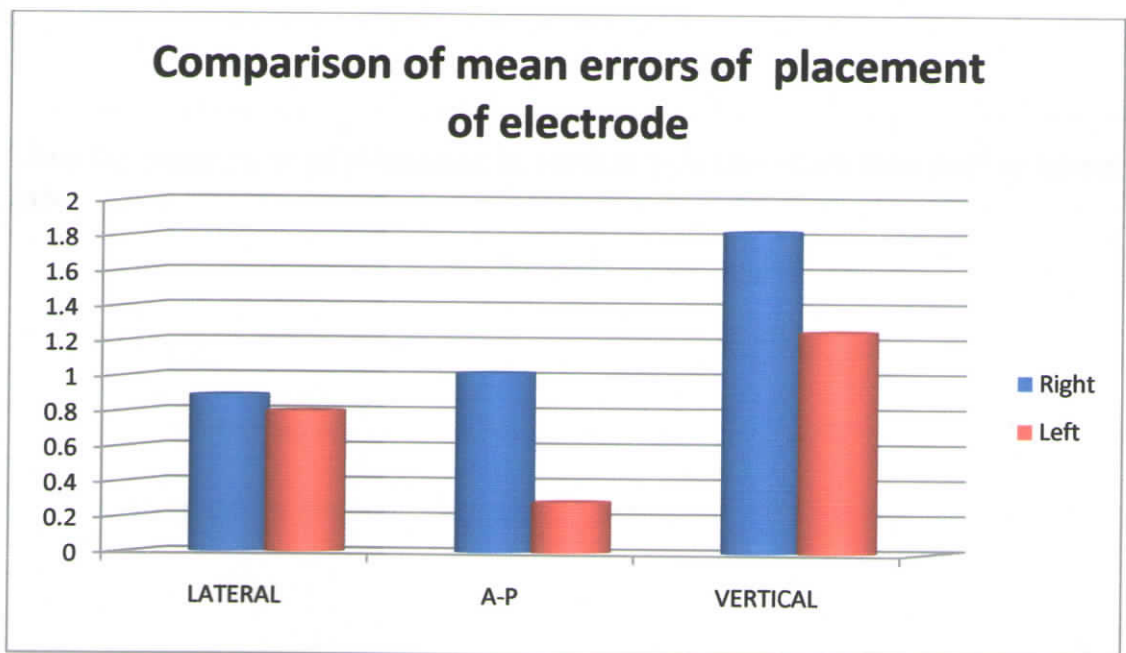
Z = 1.83 mm

LEFT SIDE (total 9 STNs)

x = 0.80 mm

y = 0.29 mm

z = 1.26 mm

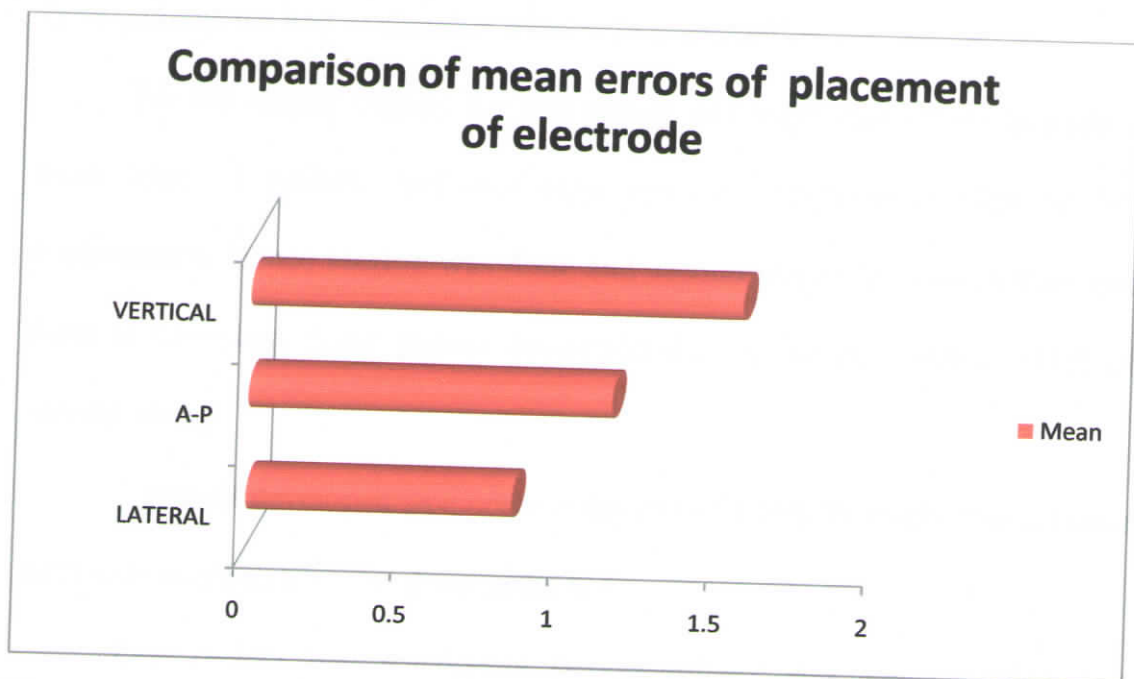


The overall mean error of 17 STN placement (differences between final intraoperative target coordinates and MR imaging-verified lead coordinates) was

X= 0.845

Y= 1.155

Z=1.565



Thus the mean error of placement in vertical axis was more than A-P or lateral axis.

COMPLICATIONS

In 1 patient frame slipped during MER hence procedure was abandoned and repeated after 3 days.

2 patients had intraoperative seizure related to pneumocephalus. In 1 of these patients we had to abandon other side implantation .

We did staged surgery for this patient and implanted other electrode 1 week later. 1 patient had confusion, agitation, restlessness after 1st left implantation, Hence staging was done and second electrode implantation was done at later date. Same patient developed deep drowsiness during MER of second sitting .

1 patient developed psychosis at the end of left STN implantation hence right side implantation was done under GA .

One patient had leucopenia postoperatively and was cephalosporin related. 1 patient had major complication in the form of intraoperative hemorrhage. He underwent evacuation of the same and EVD placement. Implants were removed .He had a stormy postoperative period . He was discharged in vegetative state . This patient was on Clopidogrel preoperatively for coronary artery disease. Thus the incidence of intracerebral hemorrhage in our study was 5%.

DISCUSSION

DISCUSSION

Retrospective analysis of 20 consecutive patients with idiopathic Parkinson's disease treated with STN deep brain stimulation at SCTIMST between October 2006 to July 2009 was carried out.

In our study mean preoperative UPDRS score was 46.25 ± 14.85 .

Mean postoperative UPDRS score was 21.94 ± 16.22 . The mean reduction in score was 24.31 ± 16.35 .

The percentage reduction was 52.56%.

Our results are comparable with studies from other centers.

In a study by J. Herzog et al.⁹⁶ at 12 months follow-up, (preoperative, 43.9 ± 15.7 ; postoperative, 18.7 ± 10.3 $P < 0.001$). UPDRS III total score was reduced by 57.5% after 12 months.

Various other studies reporting similar results are as follows:

	N	Preoperative score	Postoperative score (1year)	Reduction %
Our study	20	46.25 ± 14.86	21.94 ± 16.22	52.56
Herzog et al, 2003 ⁹⁶	32	43.9 ± 15.7	18.7 ± 10.3	57.5
Krack et al, 1997 ¹⁸³	27	63	28	55.6%
Krack et al, 1998 ¹⁸⁴	8	57.5	17.1 (6 months)	70.3%
Kumar et al, 1998 ¹⁴³	7	55.7	19.4 (6 months)	65.2%
Limousin et al, 1998 ¹⁴²	20			60
Burchiel et al, 1999 ¹³⁹	6			44
Moro et al, 1999 ¹⁴⁴	7	67.6	39.3 (16 months)	41.9%
Pinter et al, 1999 ¹⁴⁵	9	60.0	27.1	53.8%
Pillon et al, 2000 ¹⁸⁵	48	55.4	18.1	67.3%
Bejjani et al, 2000 ⁶³	12		(6 months)	70.0%
DBS/PD study group, 2001 ⁸³	96	54.0	25.7 (6 months)	52.4%
Dujardin et al, 2001 ¹⁸⁶	6	65.0	40.5	37.7%
Lopiano et al, 2001 ¹⁸⁷	20	58	25.1	56.7%
Volkman et al, 2001 ¹⁸⁸	16	56.4	22.4	60.3%
Ostergaard et al, 2002 ¹⁵¹	26	51.3	18.3	64.3%
Lagrange et al, 2002 ¹⁷⁰	60	53.7	24.3	54.7%
Simuni et al, 2002 ¹⁵³	12	43.5	23.0	47.1%
Thobois et al, 2002 ¹⁰²	14	44.9	17	62.1%
Vesper et al., 2002 ¹⁸⁹	38	48.3	24.9	48.4%
Daniele et al, 2003 ¹⁹⁰	20	58.8	30.9	47.5%

Kleiner-Fisman et al, 2003 ¹⁹¹	25	50.1	24.6	50.9%
Pahwa et al, 2003 ¹⁹²	33	43.8	26.5	39.5%
Liang et al, 2006 ¹⁹³	27	38.4	23.9	37.8%
Portman et al, 2006 ¹⁹⁴	20	46	33	28.3%
Gan et al, 2007 ¹⁹⁵	36	42.2	21.0	50.2%
Tir et al, 2007 ¹⁹⁶	100	50	29	42.0%
Witjas et al, 2007 ¹⁹⁷	40	38	12.4	67.4%
Zibetti et al, 2007 ¹⁹⁸	36	54.5	25.8	52.7%
Wider et al, 2008 ¹⁹⁹	50	47.2	24.9 (24 months)	47.3%

When we evaluated the three groups of patients of idiopathic Parkinson's disease in terms of outcome assessment [as measured by motor UPDRS] , no statistically significant difference was observed among them.

The percentage reduction in group 1 was 47.99% , group 2 was 50.99% , group 3 was 62.03 % . Group 3 shows a trend towards better reduction of motor UPDRS.

ADVERSE EVENTS

The most common adverse effect in our study is postoperative confusion and transient psychosis . In our study only 1 patient has serious adverse event in the form of intracerebral hematoma (incidence 5%)with intraventricular extension (patient was on antiplatelets preoperatively). He was

discharged in a vegetative state. 2 patients had intraoperative seizures , related to pneumocephalus.

In a study by J. Herzog et al.¹⁴¹ serious adverse effects of STN-DBS were rare. Relevant side effects necessitating surgical intervention included an intraoperative subdural hematoma without any neurological sequelae in 1 patient and minor intracerebral bleeding at the side of the trajectory of the lead was noted. Transient psychiatric symptoms were the most common therapy-related adverse effects, similar to our study.

In a data from Kenney et al¹³⁷, adverse effects noted were intraoperative Vasovagal response(2.5%), Syncope(1.2%),Severe cough 3(0.9%), IVH (0.6%),ICH (0.6), Arrhythmia (0.3%), Confusion (0.3%),Extreme anxiety (0.3%), Headache (15.0%),Confusion (5.0%), Hallucination (2.8%), Nausea/vomiting (1.6%),Seizure (1.2%), Dysarthria (0.9%), Dyskinesia (0.6%), Hypertension (0.6%), Paranoia (0.6%), Paresthesia (0.6%), Urinary retention (0.6%), Deep vein thrombosis (0.3%), Depression (0.3%), Dizziness (0.3%) Insomnia (0.3%), Pulmonary edema (0.3%), SDH (evacuated) (0.3%). Long-term (2wk) adverse effects noted were Infection (4.4%), Cognitive dysfunction (4.0%),Dysarthria (4.0%), Worsening gait (3.8%) Agitation (1.6%), Paresthesia (1.2%),Depression (0.9%),Headache (0.6%). Psychogenic tremor (0.6%),Urinary incontinence (0.6%),Blepharospasm (0.3%),Emotional lability (0.3%),Insomnia (0.3%)Metallic taste (0.3%),Suicide 1 (0.3%).

In series by Kenney's et al ¹³⁷, the most serious complications associated with DBS surgery were cerebrovascular accidents (including transient ischemic events) (0.9%), intracranial hemorrhage (1.2%), seizure (1.2%), device infection (4.4%), lead fracture (3.8%), and device movement or misplacement (3.2%)

Various other authors have reported incidences of intracerebral haemorrhages in the literature.

In a study by Pahwa et al.¹⁹³, reported incidence of intracerebral hemorrhage was 20%.

Rodriguez-Oroz et al. in 2000¹⁴⁶ in a study of 15 patients, found that 2 patients had intracerebral hematoma with incidence of 13.3 %.

Deep-Brain Stimulation for PD Study Group⁸³ studied 143 patients and reported incidence of intracerebral hematoma in 7 patients (4.9%).

Goodman et al.²⁰⁰, in a study of 100 patients found a very low incidence of only 1% of intracerebral hematoma.

In our study, the risk factor for producing intracerebral hematoma was use of antiplatelets. Hence, it is noteworthy that antiplatelets be stopped prior to DBS implantation in consultation with cardiologist and restart, once postoperative imaging has ruled out hematoma. The risk of bleeding & hematoma can also be minimised by planning a safe trajectory (avoiding sulci and ventricles) using neuronavigation machine.

We also noted that dexmedetomidine usage during surgery which we did in the last few cases enhanced patient cooperation. This drug does not reduce quality of MER recording and enhance patient tolerance of the procedure.

Using fibrin glue for fixing burr hole cap reduces incidence of pneumocephalus and fixes the cap firmly. If fibrin glue was not available blood patch (patient's own clotted blood) is a good alternative to fill the burr hole cap.

MEAN ERROR OF PLACEMENT

In our study, the mean error of placement (the mean differences between final intraoperative target coordinates and MR imaging–verified lead coordinates) is

RIGHT SIDE :

$X = 0.89$ (Total 8 STNs)

$Y = 1.02$

$Z = 1.83$

LEFT SIDE (Total 9 STNs)

$x = 0.80$ mm

$y = 0.29$ mm

$z = 1.26$ mm

The overall mean error of 17 STN placement (the mean differences between final intraoperative target coordinates and MR imaging–verified lead coordinates) in our study is

$X = 0.845$ mm

$Y = 0.655$ mm

Z=1.565 mm

The acceptable range of accuracy for placement of electrodes quoted in literature is 1 mm. We have got x and y axis placement error less than 1mm, which is fairly accurate. However we have exceeded z axis placement by 0.56 mm [Vertical axis error].

These results are comparable with other series.

In a study by Paolo Ferroli et al ²⁰¹ postoperative MR images were fused with the pre-operative stereotactic CT. The placement error in the anteroposterior, lateral and vertical planes was calculated.

The anteroposterior mean error $\pm$ SD was 0.61 ± 0.22 mm (range 0.2–0.9 mm). The lateral mean error $\pm$ SD was 0.65 ± 0.27 mm (range 0.2–2.2 mm). The vertical mean error $\pm$ SD was 0.82 ± 0.31 mm (range 0.3–1.6 mm). The vertical error is found to be slightly higher than the placement error in both the anteroposterior ($p = 0.025$) and the lateral planes ($p = 0.031$).

In our study also vertical error was significantly higher than A-P and lateral error of placement. Human error, tissular mechanic impedance, electrode mechanic impedance, frame age and maintenance certainly play a role in determining placement error.

To achieve this millimetric precision, a rigid insertion cannula has to be used. This depends upon the slice thickness . More the slice thickness, more the vertical error of placement. In addition, possible micromovements of the

electrode during the bone-fixing manoeuvres should be considered, and use of fluoroscopic control should be mandatory.

A recent study by Ruth L. O’Gorman et al¹¹⁵ proved that preoperative MRI fused with postoperative CT offers an alternative method for evaluating electrode position, but before this method can be clinically applied, the image registration accuracy must be established.

The error of registration noted by this study on MSS (Medtronic stealthstation) [which is the same machine used by us] was

$X= 0.53\pm0.47$

$Y= 0.45\pm0.43$

$Z=0.74 \pm 0.81$

In this study also vertical error was more than horizontal one.

These results are similar to results of our study.

According to by Ruth L. O’Gorman¹¹⁵ the most accurate registration protocol was that using MSS (Medtronic stealthstation).

Our study used MSS for 13 of our 20 patients and have found fairly accurate results.

The average difference between radiological and electrophysiological STN was

Right Side	LEFT SIDE
X=1.04 mm	x=1.55
Y=1.36 mm	y=1.94
Z=1.98 mm	z=2.87

For 18 STN implantations the average difference irrespective of side will be

X=1.26

Y=1.65

Z= 2.45

In a similar study by Philip Starr et al ²⁰², using similar MRI protocol as our , analysis of 76 consecutive cases of MR imaging–guided implantation of stimulators into the STN was done. In one case the lead was not implanted because an intraoperative hemorrhage occurred. To define the initial anatomical target on the basis of MR imaging, they used a hybrid of two methods: indirect targeting in which they used fixed distances from the midcommissural point and direct targeting by visualization of the STN itself.

In our study also in group 2 we used hybrid method for calculation of target. In their first 40 implantation procedures, the entry point was determined by setting the stereotactic arc and rings for a standardized approach angle of 60° from the AC–PC line in the sagittal projection and to 5 to 10° lateral from the vertical line in the coronal projection. In the subsequent 37 cases, surgical planning software was used to examine the trajectory and make slight adjustments to avoid traversing sulci or the lateral ventricle. Intraoperative MER was used along with macroelectrode stimulation for side effects. Postoperative MR images were transferred to a computer for analysis, which was performed using appropriate software (Framelink).

For the 70 procedures in which the STN was visualized, the mean and range of the AC/PC-based coordinates of the center of the STN were as follows: lateral 12.9 mm (range 11–15 mm), AP 3.5 mm (range 1 to 7 mm), and vertical 5.3 mm (range 2 to 8.5 mm).

These results are comparable with our results.

In our study of 18 STN implantation, AC-PC based coordinates of center of STN determined by MRI were

Lateral : 10.56

AP : 2.26

Vertical : 4.76.

In Starr study²⁰², the difference between radiological and electrophysiological STN was

Lateral : 0.96

AP : 0.45

Vertical : 1.07

Our corresponding values for this difference are comparable and are as follows:

X= 1.26 Lateral

Y= 1.65 AP

Z= 2.45 Vertical

According to Starr et al²⁰², differences between final intraoperative target coordinates and MR imaging–verified lead coordinates were

AP	1.62 (0–5.1)
Lateral	1.40 (0–4.7)
vertical	1.72 (0–8.8)

In our study, the mean differences between final intraoperative target coordinates and MR imaging–verified lead coordinates, in 17 STN placements were

X= 0.845 mm

Y= 0.655 mm

Z=1.565 mm

These results are statistically better and more accurate than Starr²⁰² et al. However the small sample size of our study in comparison to 77 STN electrode placements by Starr et al, makes a limitation of our study.

Axial T2 scans have less distortion when compared to coronal scans¹²⁰. Hence now we have shifted to using only axial scans for STN identification.

CONCLUSIONS

CONCLUSIONS

Although different methods can be used for targeting subthalamic nucleus, the ultimate functional outcome does not change. Subthalamic nucleus deep brain stimulation results in significantly improved functional outcome as measured by the motor UPDRS score. There is a trend for better results when nonstereotactic MRI is fused with stereotactic CT for targeting the STN. This can be a reflection of shorter "OFF" period for the patient during surgery thereby enhancing patient cooperation, allowing more time for detailed clinical evaluation of benefits and side effects thus choosing the best track for electrode implantation. Also the time allotted by the surgeon for adequate preoperative planning may reflect these results. This result may not be statistically significant because of smaller numbers.

There is a significant difference between radiologically visualised and electrophysiologically active STN. This emphasizes use of microelectrode recording and stimulation for adverse effects intraoperatively. An expert neurologist is mandatory to guide accurate localization of electrophysiological STN.

The practice of doing preoperative stereotactic MRI scan on the day of surgery prolongs operative time by adding the time taken for the MRI to the actual procedure. This also prolongs the total time patient is OFF drugs.

Preoperative non stereotactic MRI done a few days before the day of surgery allows the surgeon adequate time for planning.

Stereotactic CT scans done on the day of surgery hastens the procedure as this can be completed in a very short time as compared to MRI. Thus it saves precious time on the day of surgery and also gives better patient compliance as patient has to wear the frame for a short time as compared to stereotactic MRI. The fusion of stereotactic CT with nonstereotactic MRI combines the advantage of superiority of MRI to anatomically visualize STN and property of CT to reduce distortion artefacts and provide accurate bony landmarks. A safe trajectory can be planned once the target is decided using stealth station, avoiding sulci and ventricles , thus minimizing intraoperative hemorrhagic complications.

Fusing nonstereotactic MRI with stereotactic CT scan is accurate as shown in this study. Hence stereotactic MRI can be avoided.

This approach is relatively safe, time efficient and accurate. Microelectrode mapping results in a major change in the final location of the DBS lead.

Use of postoperative CT also saves time and avoids patient discomfort with framebased MRI . Fusion of preoperative MRI and postoperative CT is very effective to assess accuracy of electrode placement and gives correct position of postoperative CT artefact in relation to target STN seen on

preoperative MRI. The fused postoperative CT/preoperative MRI may encompass the benefits of both modalities, offering an alternative method for evaluating electrode position relative to the target structures, without the need for postoperative MRI. CT/MRI fusion provides a safe, practical technique for accurate postoperative identification of DBS electrodes, which is mandatory for ultimate better functional outcome of patient.

The vertical error of placement is higher than lateral and anteroposterior error and can be minimised by use of rigid insertion cannula, strict use of fluoroscopic control and avoiding undue movement during electrode fixing maneuvers.

Use of Dexmedetomidine can be suggested as a sedative during the surgery as it does not interfere with MER and also enhances good patient cooperation.

Use of advanced technologies like stealth station machine and FRAMELINK software can give more accurate registration protocols, provide point to point merging, save precious time and also minimise human errors, to achieve milimetric precision, which is very vital for successful deep brain stimulation electrode placement.

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PROFORMA

PROFORMA

1. Name
2. Hospital . no
3. Age
4. Sex
5. Preoperative symptom duration in years
6. Tremor Y/N
7. Rigidity Y/N
8. Bradykinesia Y/N
9. Levo-Dopa responsiveness : Y/N
10. Add on medication:
11. Dopa induced dyskinesia: Y/N
12. Date of surgery
13. Preoperative motor UPDRS score : Drug on
Drug off
14. Postoperative motor UPDRS score at 1year: Battery on drug off :
Battery on drug on :
15. Preoperative stereotactic MRI/ CT:
- 16 Postoperative CT/MRI:
- 17 GROUP: 1 2 3
- 18 Single stage / Double stage:
- 19 Calculated STN stereotactic coordinates(Radiologic STN)

Right STN	left STN
X	x
Y	y
Z	z
- 20 Intraoperative MER recording
 - a. Number of tracks obtained
 - b. Track chosen for implantation
 - c. Reason for choosing the track

21 Coordinates of MER track chosen for implantation
(Electrophysiological STN)

Right side	left side
TX	Tx
TY	Ty
TZ	Tz

22 Difference between radiologic and electrophysiological STN(X-TX)

Right side	left side
X	x
Y	y
Z	z

23 Postoperative MRI coordinates of DBS electrode artifact

Right DBS electrode	left DBS electrode
PX	Px
PY	Py
PZ	Pz

24 Difference between electrophysiological and postoperative STN
(TX-PX) Error Of Placement

Right side	left side
X	x
Y	y
Z	z

25. Complications:

ABBREVIATIONS

STN: Subthalamic nucleus

PD: Parkinson's disease

DBS: Deep Brain Stimulation

GPI : Globus Pallidus Pars Interna

VIM: Ventralis Intermedius Nucleus

AC : Anterior Commissure

PC: Posterior Commissure

RN: Red Nucleus

SNR: Substantia Nigra

CT: Computed Tomography

MRI: Magnetic Resonance Imaging

MER: Micro Electrode Recording

MCP: Midcommissural Point

IPG: Implantable Pulse Generator

SD: Standard Deviation

ICH: Intracranial Hemorrhage

SDH: Subdural Hematoma

IVH: Intraventricular Hemorrhage

UPDRS: Unified Parkinson's Disease Rating Scale

GA: General Anaesthesia

EVD: External Ventricular Drain