

Exploring the Human Brain Using Single-unit Microelectrode Technique during Awake Stereotactic Functional Neurosurgery

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Abstract

In neuroscience research, the use of true single-unit microelectrode technique has been confined largely to the animal neurophysiology laboratory due to the complexity of the equipment required and the fastidious, time-consuming nature of the methodology. We report here our successful clinical use of this technique in human patients with Parkinson's disease undergoing awake stereotactic movement disorder neurosurgery. The common targets in such operations are the postero-ventral portion of the globus pallidus interna in the basal ganglia (for dopa-induced dyskinesias particularly) and the ventro-intermediate nucleus of the thalamus (for tremor-predominant Parkinson's disease).

Accurate and exquisite neurophysiological localisation of these small targets deep within the brain can be obtained with single-unit microelectrode technique prior to the insertion of a deep brain stimulator or definitive neurosurgical radiofrequency lesioning in the target area. This accuracy translates into better outcomes for patients and a reduced incidence of complications. The wealth of data gained from studying the abnormal behaviour of neurons within the basal ganglia and thalamus also provides us with fundamental insights into the pathophysiology behind Parkinson's disease.

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Introduction

Neurophysiology research using single-unit microelectrode technique was pioneered by the Nobel Prize-winning neuroscientist David Hubel.¹ Studying the visual cortex of cats and monkeys with this technique, he and Torsten Wiesel discovered fundamental features of the organisation of the visual cortex, for which they were awarded the Nobel Prize in 1981.

Use of this technique has remained largely confined to basic neuroscience researchers within the province of animal neurophysiology research laboratories. It has not seen widespread clinical application in humans. This is due primarily to the complexity of the equipment required to support true single-unit microelectrode recording and microstimulation, as well as the necessity for staff to be specially trained, and academically inclined towards using this fastidious and time-consuming technique, which is the present gold standard in neurophysiological localisation.²

We report here some preliminary results of our successful clinical use of this sophisticated methodology in patients with Parkinson's disease undergoing awake stereotactic movement disorder neurosurgery. Microelectrodes were used in these patients to definitively localise small target areas deep within the brain in the basal ganglia and thalamus prior to the insertion of a deep brain stimulator or definitive radiofrequency lesioning. Typically, these targets would be (1) the postero-ventral part of the globus pallidus interna in the basal ganglia (for dopa-induced dyskinesia particularly) and (2) the ventro-intermediate nucleus of the thalamus (for the tremor-predominant type of Parkinson's disease).

Methods

Our operative methodology involves the following sequential steps:

1. Placement of magnetic resonance imaging (MRI)-

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- compatible CRW (Cosman-Roberts-Wells) stereotactic frame under local anaesthesia;
2. Radiological imaging of the brain (MRI) with the stereotactic frame on;
 3. Computer planning of the surgery done on a Silicon Graphics Reality Engine Workstation (where a resident Electronic Brain Atlas is installed) with the radiological data obtained;
 4. Surgery proper involving
 - (i) microelectrode exploration and mapping of the target area (via microrecording and microstimulation) and
 - (ii) definitive therapeutic radiofrequency lesioning or insertion of a deep brain stimulator once the precise target is found after neurophysiological single-unit microelectrode mapping of the area.

Step 1: Frame Placement

This is done under local anaesthesia as the patient needs to be fully awake and co-operating with the neurosurgeon during the operation when localising the target area during microelectrode mapping of the area as well as during radiofrequency lesion-making or deep brain stimulation when the target area is found. A Radionics MRI-compatible CRW stereotactic frame with localising fiducials is attached to the patient's head with the base placed as far as possible parallel to the orbito-meatal plane, which approximates the AC-PC (anterior commissure-posterior commissure) plane. Frame placement is fastidiously done (unlike general stereotaxy), but this usually takes no more than 5 to 10 minutes to do. The patient is then transferred into the MRI scanner for neuroimaging.

Step 2: MRI Scanning

A 1.5 Tesla MRI scanner (Signa Horizon; General Electric, Milwaukee) is used in our institution. Sagittal T1-weighted spin-echo localiser scans are performed first to identify the anterior and posterior commissures. If necessary the head tilt is adjusted such that the AC-PC line and midline falx are in the true horizontal and vertical orthogonal axes. Axial three-dimensional Fast Gradient Recalled Echo (3D FGRE) study is then performed at 1 mm slice thickness from the level of the middle cerebellar peduncle to above the level of the corpus callosum. A square field of view (28 × 28 and matrix of 256 × 256) is used to facilitate subsequent reconstruction and reformatting of the images. This acquisition of 60 contiguous slices takes about 11 minutes. The images are then transferred via an ISDN line to a Silicon Graphics Reality Engine Workstation where reformatting is then done in two and three dimensions. We also perform 3D FGRE examinations in the coronal and sagittal planes through the basal ganglia using contiguous 2 mm thick slices with the same field size and matrix. Even in patients with a head tremor we have not had

much problems with image definition using the above scanning technique.

Step 3: Surgery Planning on Computer Workstation

The Electronic Brain Atlas developed by one of the authors (WLN) from the Institute of Systems Science, National University of Singapore, is used for atlas-based functional neurosurgery planning.^{3,4} It runs on a high-end Silicon Graphics Reality Engine Workstation Computer. The system is based on a deformable electronic version of Atlas of Stereotaxy of the Human Brain by Schaltenbrand and Wahren.⁵ The Schaltenbrand-Wahren atlas microseries are digitised, enhanced, segmented, labelled, aligned and organised into atlas volumes. They are mutually pre-registered, and three-dimensional models of the structures are constructed. The atlas may be interactively registered with actual patient's data. A computer system has been developed which provides data interpolation, reformatting, registration, visualisation, mensuration, and path display and editing in two and three dimensions.^{6,7} Surgical planning on the computer workstation involves the following sequential steps: (a) reformat patient data, (b) register globally with brain atlas, (c) register locally with brain atlas, (d) plan target coordinates and (e) plan path and entry point coordinates.⁸

Actual patient's data are first reformatted if they are not acquired in the AC-PC plane. They are then registered globally with the deformable electronic brain atlas based on the Talairach global registration (i.e. proportional grid system transformation).⁹ The accuracy of registration within a region of interest is then enhanced by use of any local landmarks. This completes the registration procedure (Fig. 1). The neurosurgeon can then navigate in the atlas-data space as well as plan the target(s) and entry point(s) in two and three dimensions.

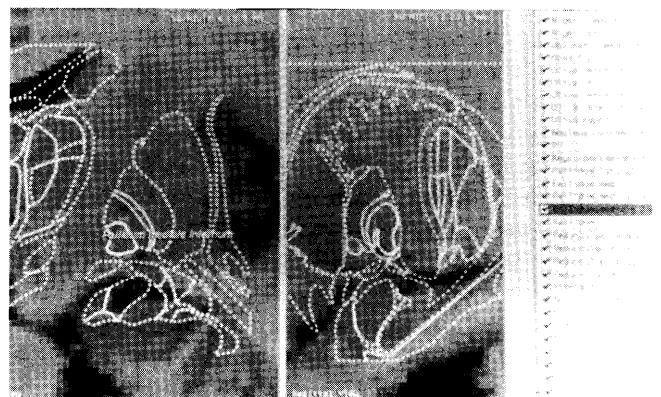


Fig. 1. Electronic Brain Atlas being used for localising a pallidal target: The outlines of the basal ganglia and thalamus are coregistered globally and locally with the patient's magnetic resonance imaging scans (left: coronal view; right: sagittal view). The globus pallidus interna is highlighted.

Step 4: Operation Procedure Proper

After preoperative planning on the workstation is completed, the operation proper is commenced in the operating room. A pre-coronal frontal burr hole is usually made under local anaesthesia. This is usually 20 mm lateral to the sagittal midline for a pallidal target and 15 mm lateral to the sagittal midline for a thalamic target. The microelectrode trajectory is in the true sagittal plane of the burr hole as this allows the most accurate mapping to be performed using the sagittal slices of the Schaltenbrand and Wahren brain atlas.

The operation itself then comprises the following two stages:

- A) neurophysiological single-unit microelectrode mapping of the radiologic/anatomic target to definitively localise and confirm that the target chosen is indeed the specific target, characterised by its individual neurophysiological "signature"; and
- B) therapeutic radiofrequency lesioning or insertion of a deep brain stimulator once the target is localised.

Stage A: Single-Unit Neurophysiological Localisation

The Atlantic Research System (ARS) NeuroSystem-2 Micro-Electrode Guided Neurosurgical System is used for neurophysiological localisation. A high impedance 1.5' Mega Ohm glass-coated platinum-iridium microelectrode with a tip diameter of one micron is employed. This is inserted (protected by a fine outer sheath cannula) into the brain at a trajectory of 60° to the AC-PC plane. Microrecording is usually started from 20 mm superior to the target and extended to about 10 to 15 mm below the target. The microelectrode is mounted on a high precision micro-positionable platform (Fig. 2). This platform provides quick and accurate micro-positioning during mapping. Errors introduced by repetitive stereotactic frame positioning are eliminated. An electronic microdrive is used to advance the microelectrode submillimeter by submillimeter. This provides a most economical and direct method for microelectrode positioning. A remote probe connects directly to the microelectrode. This is a preprocessor section for all neural data that will be collected by the data collection system or heard through the audio system. An integrated AC differential amplifier (with impedance checking capabilities) is connected to the remote probe. A dual window discriminator with analog delay is used for single neural unit identification and data display triggering. Audio detection of neural cell discharge is critical to proper brain mapping and the audio processing section consists of a dual channel high fidelity amplification circuit along with frequency equalisation. The unit allows the user to selectively adjust the gain or attenuation of selected audible frequencies. The audio output is available at the output amplifier for head phone or speaker presentation and to the data

recording section for archive and post processing recording. The data display consists of 2 digital/analog oscilloscopes, one for viewing the raw neural output from the electrophysiological monitoring systems and the other for monitoring the discriminated neural unit. The entire system is console-rack mounted and is modular by design (Fig. 3).

Stage B: Definitive Therapeutic Procedure

Once the target has been definitively localised and defined using the above microelectrode technique, definitive therapeutic radiofrequency lesioning of the target (Fig. 4) or insertion of a deep brain stimulator in the target area is then done. The patient is usually required to be awake and co-operating with the neurosurgeon during this important final part of the operation in order to ensure optimal lesion or stimulating electrode placement with minimal side effects and complications to the patient. This concludes the operative procedure.

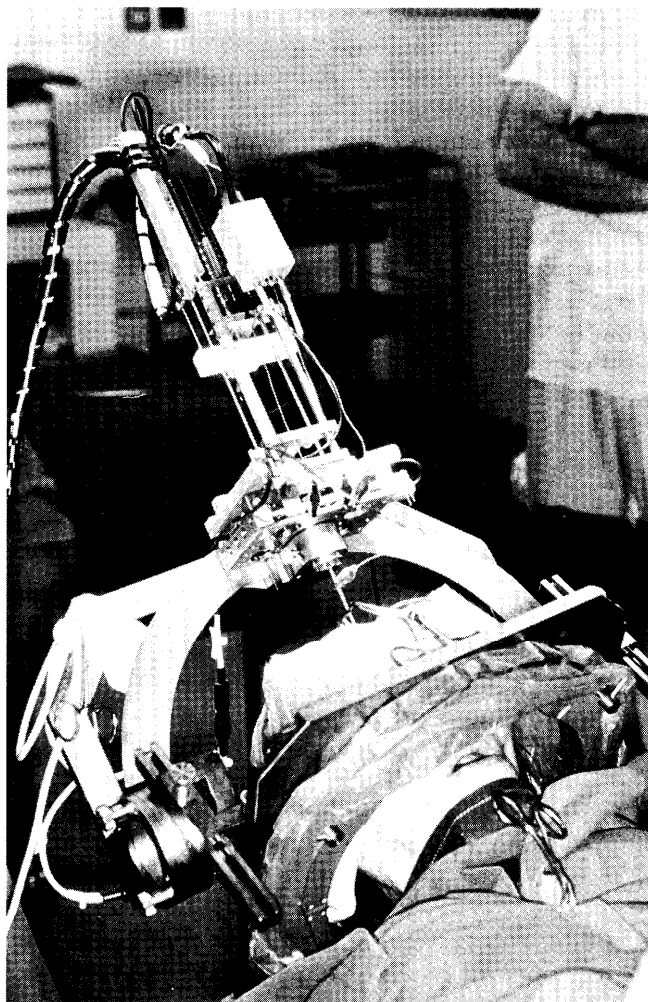


Fig. 2. The 3-dimensional Micropositioning Headstage specially adapted to fit on to the CRW (Cosman-Roberts-Wells) stereotactic frame and supporting single-unit microelectrode-guided functional neurosurgery. This platform provides quick and accurate micro-positioning during the mapping procedure.

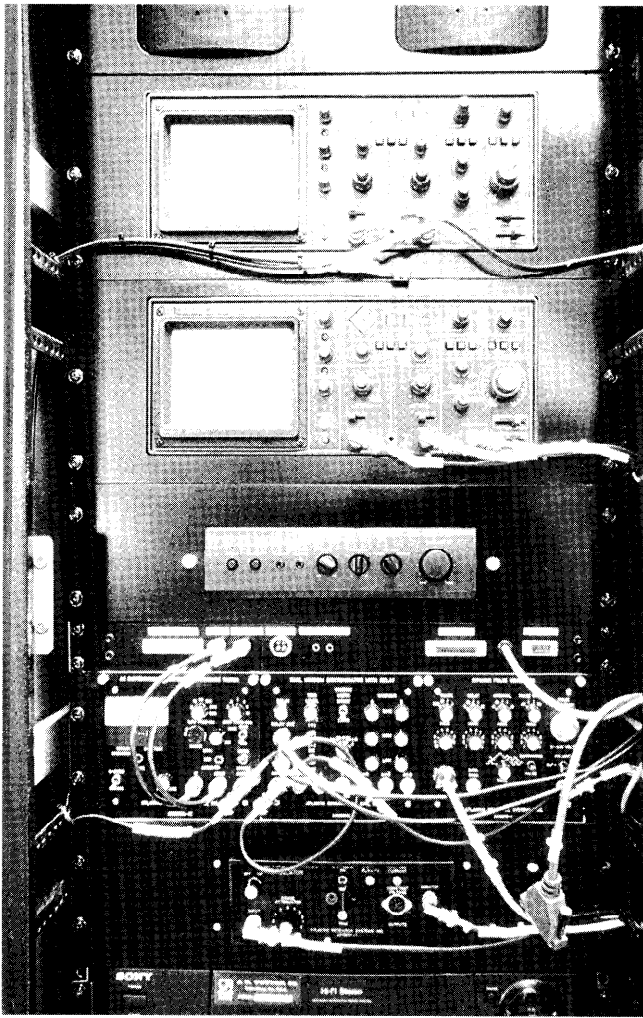


Fig. 3. Part of the complex, sophisticated, modular, rack-mounted equipment used for single-unit microelectrode work (see text for description).

Results

In general, the microelectrode findings in humans with Parkinson's disease closely parallel those found in MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-treated monkeys.¹⁰⁻¹² In Parkinson's disease, segments of the globus pallidus show alterations in neuronal activity which are believed to underlie the cardinal symptoms of tremor, rigidity and akinesia. Specifically, the mean spontaneous ongoing firing rate in globus pallidus externa (GPe) is decreased and that in globus pallidus interna (GPi) is increased. The distinctive neuronal firing patterns within the putamen, globus pallidus externa and globus pallidus interna permit precise and exquisite physiological localisation using single-unit microelectrode technique.

Some of these typical single-unit findings found in our patients are summarised below (Fig. 5):

1) In GPe, cells with a 10 to 60 Hz spontaneous discharge rate interrupted by pauses ("pauser cells") were seen.



Fig. 4. Right pallidotomy for dopa dyskinesia: Postoperative magnetic resonance imaging scan showing a radio frequency lesion perfectly placed within the postero-ventral portion of the globus pallidus (arrow) using microelectrode-guided stereotactic technique.

- 2) Some cells within GPe were fired in a low frequency burst (LFB) fashion.
- 3) Border cells between GPe and GPi have a 30 to 40 Hz firing pattern.
- 4) Globus pallidus interna is characterised by cells firing continuously at 200 to 500 Hz.
- 5) Optic tract is characterised by an absence of cellular activity and axons identified by their narrow monophasic spikes. Microstimulation in optic tract evoked visual sensation at low thresholds (5 to 10 microamps usually).
- 6) In the lower half of the ventrointermediate (Vim) nucleus of the thalamus, neurons respond to contralateral passive joint movement, squeezing of muscle bellies, or pressure on other deep structures, such as tendons and subcutaneous tissue.
- 7) In patients with tremor, there are some kinesthetic cells (i.e. cells which fire in response to joint movement) which also fire rhythmically at the patient's tremor frequency.

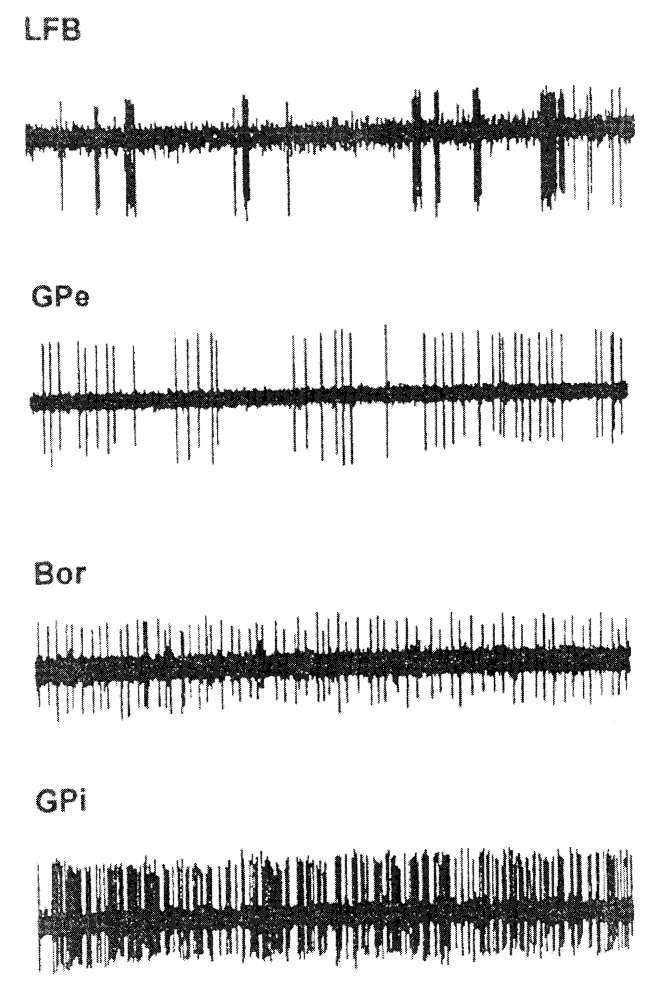


Fig. 5. Typical single unit findings during microelectrode recording in the globus pallidus of patients with Parkinson's disease. From top to bottom: Low frequency burst (LFB) cells in the globus pallidus externa; globus pallidus externa characterised by cells firing at 10 to 60 Hz with pauses ("pauser cells"); border (Bor) cells between GPe and GPi with a characteristic 30 to 40 Hz firing pattern; GPi with cells firing at high frequency (200 to 500 Hz).

Discussion

The application of true single-unit microelectrode technique in humans (with the exquisite ability to discriminate single neurons) is used by only a minority of academic neurosurgical centres in the world.^{2,13} The Tan Tock Seng Hospital Brain and Spine Centre is the first centre in Asia (outside of Japan) to use this technique routinely in all their movement disorder cases that come for stereotactic neurosurgery. Our preliminary results using this methodology is the subject of this brief report. The precision with which we are able to localise target areas (like the globus pallidus interna in the basal ganglia and the ventro-intermediate nucleus in the thalamus) neurophysiologically with this technique is unsurpassed. This is of great help and importance to the functional neurosurgeon as it affords him very precise knowledge of the anatomical boundaries (confirmed

via neurophysiology) of the deep brain structures he is exploring. The very detailed neurophysiological mapping of the target area aids immensely in the final decision making as to where is the best site in the brain to insert a deep brain stimulator or place a radiofrequency lesion.

This is best exemplified in the case of a postero-ventral pallidotomy where in order to obtain the best clinical result, the radiofrequency lesion has to be precisely placed within the sensori-motor part of the globus pallidus interna (i.e. the postero- and ventral-most portion of the globus pallidus interna).¹⁴ If the lesion is too posterior, it encroaches on the internal capsule, damage of which will cause a hemiparesis or hemiplegia. If the lesion is too ventral, the optic tract will be damaged and a permanent hemianopia will result. The use of microelectrodes allows us to precisely delineate and define the borders of GPi and identify unequivocally the internal capsule and optic tract and hence avoid lesioning these areas. We are also able to precisely identify the sensorimotor part of GPi by the response of neurons there to modulation by eyes, mouth and joint motion. Typically 3 to 5 microelectrode tracks are required to fully map out the area satisfactorily before radiofrequency lesion placement is done. Anatomical imaging [Computed Tomographic (CT)/MRI scan with help from the Electronic Brain Atlas] serves only as a guide to the approximate target location, while single-unit neurophysiological mapping and localisation remains the "gold standard" and provides us with the definitive information on where the exact location of the final chosen target area is. Figure 4 shows a postoperative MRI scan of one of our patients who underwent a right-sided microelectrode-guided pallidotomy primarily for dopa-induced dyskinesias. Three microelectrode tracks were used in this classical case to map out the area neurophysiologically. The optic tract, internal capsule and boundaries of the globus pallidus interna were clearly identified before definitive radiofrequency lesioning was done. The postoperative MRI scan shows that the radiofrequency lesion has been precisely placed in the ideal spot: the postero-ventral portion of the globus pallidus interna.

In tremor-predominant Parkinson's disease, the presence of kinesthetic cells and tremor cells (revealed using single-unit microelectrode recording technique) allows us to identify the Vim nucleus of the thalamus with confidence. This nucleus is the usual target for eliminating the tremor in Parkinson's disease and from other causes. Placement of a deep brain stimulator or a radiofrequency lesion accurately in this area will usually stop a patient's tremor, be it from Parkinson's disease, essential tremor, post-trauma or multiple sclerosis (although surgery usually has the best results in Parkinson's disease).

The neurophysiological technique described in this article requires an experienced single-unit neurophysiologist to be present during the entire intraoperative mapping phase in order to ensure an excellent fidelity from the microrecordings. All clinical decisions made (based largely on the microelectrode findings) rest with the neurosurgeon, of course.

We believe that the extra time and expenses incurred, as well as the specialised and highly skilled manpower required for this technique, are all well worth the investment and effort, due largely to the great level of finesse which the technique brings to the operating room in terms of neurophysiological localisation. Lozano et al¹⁵ in their study found that a MRI localised stereotactic target for a pallidotomy was often too posterior and inferior to the best placement, as determined by the results obtained with microelectrode recording and microstimulation. There was little revision of co-ordinates in only 4 of their 26 reported cases. Also, using microelectrode technique, their incidence of optic tract damage was 0% compared to 14% in Laitinen's series¹⁶ where microelectrodes were not used. Finally, the wealth of single-unit data gathered for research is enormous utilising this technique, and it is very useful for post-procedural off-line analysis and research into the fundamental abnormalities present in single neurons of the brains in patients with Parkinson's disease.

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REFERENCES

- Hubel D H. Tungsten microelectrodes for recording from single units. *Science* 1957; 125:549-50.
- Tasker R R, Lenz F A, Yamashiro K, Dostrovsky J O. Microelectrode techniques in localization of stereotactic targets. *Neurol Res* 1987; 9:105-12.
- Nowinski W L, Fang A, Nguyen B T, Raphel J K, Jagannathan L, Raghavan R, et al. Multiple brain atlas database and atlas-based neuroimaging system. *J Image Guided Surg* (In press).
- Nowinski W L, Fang A, Nguyen B T, Raghavan R. Talairach-Tournoux/Schaltenbrand-Wahren based electronic brain atlas system. *Lecture Notes in Computer Science*. Vol 905. Berlin: Springer-Verlag, 1995:257-61.
- Schaltenbrand G, Wahren W. Atlas for Stereotaxy of the Human Brain. Stuttgart: Thieme, 1977.
- Yeo T T, Nowinski W L. Functional neurosurgery aided by an electronic brain atlas. *Acta Neurochir (Wien)* 1996; 138:613-5.
- Yeo T T, Nowinski W L. Movement disorder surgery guided by electronic brain atlas. *Mov Disord* 1996; 11(Suppl 1):103.
- Yeo T T, Nowinski W L. Functional neurosurgery aided by use of an electronic brain atlas. In: Broggi G, editor. *Advances in Stereotactic and Functional Neurosurgery*. Berlin: Springer Verlag, 1997 (In press).
- Talairach J, Tournoux P. Co-Planar Stereotactic Atlas of the Human Brain. Stuttgart, New York: Georg Thieme Verlag/Thieme Medical Publishers, 1988.
- Vitek J, Kaneoke Y, Turner R, de Long M. Neuronal activity in the internal (GPi) and external (GPe) segments of the globus pallidus (GP) of Parkinsonian patients is similar to that in the MPTP-treated primate model of parkinsonism [abstract]. *Soc Neurosci* 1993; 19:1584.
- Filion M, Tremblay L. Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced Parkinsonism. *Brain Res* 1995; 547:142-51.
- Sterio D, Beric A, Dogali M, Fazzini E, Alfaro G, Devinsky O. Neurophysiological properties of pallidal neurons in Parkinson's disease. *Ann Neurol* 1994; 35:586-91.
- Lenz F A, Dostrovsky J O, Kwan H C, Tasker R R, Yamashiro K, Murphy J T. Methods for microstimulation and recording of single neurons and evoked potentials in the human central nervous system. *J Neurosurg* 1988; 68:630-4.
- Lozano A M, Lang A E, Galvez-Jimenez N, Miyasaki J, Duff J, Hutchinson W D, et al. GPi pallidotomy improves motor function in patients with Parkinson's disease. *Lancet* 1995; 346:1383-6.
- Lozano A, Hutchinson W, Kiss Z, Tasker R, Davis K, Dostrovsky J. Methods for microelectrode-guided posteroventral pallidotomy. *J Neurosurgery* 1996; 84:194-202.
- Laitinen L V, Bergenheim A T, Hariz M I. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *J Neurosurg* 1992; 76:53-61.