Functional neurosurgery

The modulation of neural and mind circuits

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ABSTRACT

يوجد مجموعات مختلفة من الدوائر المعقدة التركيب من الخلايا العصبية والكيميائية العصبية التي تعمل على تنظيم السلوكيات ووظائف الدماغ. ويولد أي اختلال في هذه الدوائر اضطرابات عصبية وظيفية مثل اضطرابات الحركة، والذاكرة، والاضطرابات النفسية، كما قد يؤدي إلى حدوث مرض الصرع وأمراض الألم المزمن. تساهم جراحة الأعصاب الوظيفية في استعادة الوظائف الطبيعية عن طريق إزالة الخلايا العصبية الغير طبيعية أو تعديل وظيفة الدوائر المسببة للاضطرابات العصبية. تعد جراحة تعديل الوظائف العصبية حقلاً سريع التطور يصحبه تطورات هائلة في مجال التصوير العصبي والتكنولوجيا الحديثة. سوف نناقش في هذا البحث التطورات والآفاق الجديدة في مجال الجراحة العصبية الوظيفية.

Different complex neuroanatomical and neurochemical circuits regulate a variety of neuronal behaviors and brain functions. Any disturbance in these circuits can generate functional disorders such as movement disorders, epilepsy, pain, memory disorders, and psychiatric disorders. Functional neurosurgery aims to restore these functions, either by removing or isolating the abnormally behaving neurons or by modulating the disturbed circuits. Neuromodulation is a fast-growing field, powered by the recent advances in neuroimaging and technology. Here, we discuss recent advances and new horizons in functional neurosurgery.

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Surgery may be used to treat functional neurological disorders by altering and modulating abnormally functioning neuronal circuits and physiological activities. There are many clinical indications for functional neurosurgery, including movement disorders, epilepsy, pain, psychiatric disorders, addiction, memory disorders, and other conditions.[1] Many brain circuits are accessible to functional surgery. Over the evolution of functional neurosurgery, techniques for interrogating and modulating brain circuits have become preferable to ablative or resective surgery. Basic neuroscience research has both motivated and benefited from several functional surgery techniques that allow the exploration of targets deep within the brain. On the other hand, advances in functional neuroimaging, technology, and neurosciences have had a significant impact on the rapid growth of functional neurosurgery. Here, we review the evolution and clinical applications of this field.

Historical overview. Functional neurosurgical procedures for the management of neurological and behavioral disorders were developed prior to the introduction of stereotactic frames and surgery. At the end of the 19th century, Horsely and colleagues[2,3] performed the first resective procedure to treat hyperkinetic movement disorder. Their procedure involved the resection of the motor cortex to treat athetotic movement. In 1912, the French surgeon, Lirche,[4] performed cervical rhizotomy to treat Parkinsonian tremor. Subsequently, several resection procedures have been used to control certain types of movement disorders.[5,6] Russell Meyers[7,8] pioneered procedures that target the basal ganglia to treat movement disorders. In 1939, he excised part of the caudate nucleus to treat Parkinsonism. By the end of the 1940s, he had operated on 58 patients with different movement disorders and observed improvement in 60%

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of the cases, although the mortality rate was as high as 12%.[7] The concept of stereotactic surgery arose after the introduction of several stereotactic frame apparatuses. In 1890, the Russian anatomist Zernov[9-11] developed a map of the human cerebral cortex correlated with the cerebral functional areas. Two years later, Altukhov[12] further refined Zernov's work in humans. Several investigators consider Zernov's apparatus to be the first stereotactic apparatus used in clinical practice,[13-17] although some Western authors disagree.[1] Nevertheless, Zernov's work is considered as one of the most important early works in the field of stereotactic surgery. In 1873, Dittmar[18] used a guided probe to approach the medulla oblongata in an animal model. Horsely and Clarke[19] described their stereotactic apparatus in 1908. This apparatus was used for animal studies; however, they gave a detailed description of the lateral (X), anterior-posterior (Y), and craniocaudal (Z) Cartesian coordinates, which remain the basis of stereotactic surgery. This work was not translated to human applications for several decades until Spiegel and Wycis[20,21] reported the first stereotactic pallidotomy in a patient with Huntington's disease. The procedure was termed "stereoencephalotomy".[20,22] The principles used in this procedure were maintained for many years by most stereotactic neurosurgeons. In 1948, Leksell[23] designed the first arc-centered stereotactic frame. Subsequently, several different stereotactic devices and grids were created by many investigators, including Hecaen et al,[24] Riechert and Wolff,[25] Baily and Stein,[26] Narabayashi,[27,28] Zamorano et al,[29] Brown and Roberts,[30] Laitinen et al,[31] and Patil.[32] Stereotactic frame development led to several different lesioning procedures targeting the basal ganglia and the thalamus to treat tremor and rigidity, employing a variety of surgical techniques and target locations.[33-36] The ventral-posterior globus pallidus internus and motor thalamus were found to be the optimal targets for symptom control. At that time, ablation methods included leucotomy; chemical methods utilizing, for example, alcohol and glycerol; and radiofrequency treatment. Cooper[37] advocated the ligation of the anterior choroidal artery to treat Parkinsonism. However, due to the high complexity of this procedure, he shifted to an ablative procedure using direct alcohol injection into the pallidum, which he termed "chemopallidectomy".[38] It was estimated that 25000 stereotactic procedures had been performed by 1965.[39] In the 1960s, the significant clinical benefit of L-dopa led to a dramatic reduction in surgical procedures to treat Parkinson's disease (PD). For almost 2 decades, surgery for movement disorders was limited to the treatment of tremor and dystonia. In the 1980s, the realization of the limitations and side effects of PD medications generated renewed interest in ablative procedures for the treatment of PD. On the other hand, the detailed descriptions of the thalamic

nuclei by Hassler et al,[40] Macchi and Jones,[41] and Schaltenbrand and Wahren,[42] and of the basal ganglia circuits by Delong et al,[43] paved the way for new therapeutic targets for stereotaxis. Electricity has been used for many centuries to treat various neurological and behavioral disorders. In the first century AD, electricity from the torpedo fish was used to treat epilepsy.[44] In 1803, Aldini used Volta's device to electrically stimulate the body of a hanged criminal.[45,46] In 1874, Bartholow[47] electrically stimulated the cerebral cortex during surgical removal of a brain abscess. Early observations revealed that intraoperative acute stimulation of the thalamus and pallidal stimulation reduce tremor.[40] This observation, in addition to the success of electric stimulation to treat pain, established chronic deep brain stimulation (DBS) as a legitimate treatment for movement disorders. The first application of chronic DBS to treat movement disorders was carried out in Russia by Bechtereva et al.[48] They implanted electrodes with external connectors, and the patients were required to make recurrent visits over the entire stimulation course. Subsequently, Brice and McLellan[49] used a fully implanted thalamic stimulator to treat intention tremor in 2 patients. The clinical efficacy of chronic DBS to treat movement disorders has been reported by Blond and Siegfried,[50] and Benabid et al.[51,52] These reports established a new standard in the field of functional neurosurgery for movement disorders, and neurostimulation began to replace ablative procedures in many centers throughout the world.

Horsley[53] performed the first surgical intervention for the amelioration of epileptic seizure, carrying out cortical resection in a patient suffering from post-traumatic epilepsy. Cortical resection to treat epilepsy has since been performed by several other surgeons.[54,55] After the invention of electroencephalography (EEG) by Hans Berger in 1929,[56] EEG and electrocorticography were used by Penfield and Jasper[57,58] to tailor resective surgeries for epilepsy. Electrodes were implanted for chronic recording of cortical activity to identify the epileptic focus. Despite the availability of resective surgery, many patients were not candidates for this type of therapy, and resective surgery failed to cure epilepsy in a significant number of patients who underwent this procedure. Thus, several investigators were motivated to create alternatives to resective surgery to treat more patients with pharmacoresistant epilepsy. Cooke and Snider[59] reported an arrest of focal seizures after stimulation of the cerebellar cortex. In 1973, Cooper et al[60] performed the first trial of chronic neurostimulation to treat epilepsy and suggested that there was a reduction in seizure frequency after subdural cerebellar stimulation. Subsequent researchers have carried out stimulation trials targeting several deep brain structures including the centromedian thalamic nucleus,[61-74] anterior thalamus,[75-82] caudate

nucleus,[83-85] subthalamic nucleus,[86-92] mammillary body,[93,94] amygdalohippocampal complex,[69,95-107] locus ceruleus,[108] and, more recently, the mammillothalamic tract.[109] In addition to the stimulation of cerebral structures, the stimulation of peripheral nerves, particularly the vagus nerve, has become the most widely used neurostimulation strategy to treat epilepsy. In 1938, Baily et al[110] provided the first evidence that the inhibition of the nucleus tractus solitarius (NTS) could reduce susceptibility to limbic motor seizures in animals. Zabara[111] published the first report of vagal nerve stimulation (VNS) and its utility in the treatment of epilepsy. The first VNS system was implanted in a human in November 1988.[112] Subsequently, many studies have evaluated the efficacy and safety of VNS.[113] Currently, responsive neurostimulation is a top priority in epilepsy research. This system provides automated real-time seizure detection and delivers stimuli to the region of the suspected seizure origin (in a contingent or closed-loop system). Osorio et al[114] investigated the feasibility, safety, and efficacy of the closed-loop system with promising results. The VNS is the only electrical stimulation treatment method for epilepsy that has been approved by the United States Food and Drug Administration (FDA). Anterior thalamic stimulation was recently recommended for approval by the FDA advisory panel.[113]

Similar to the trend in movement disorder surgery, there has been a progressive move toward neuromodulation procedures, such as electrical stimulation and drug delivery, to treat pain disorders. The success and widespread use of DBS therapy led to several clinical trials associated with the treatment of other disorders including some psychiatric illnesses, Alzheimer's disease, and addiction. Moreover, stereotactic radiosurgery has increasingly been used to treat several neurological functional disorders such as trigeminal neuralgia and tremor. **Table 1** summarizes the clinical applications of functional neurosurgery. In the following sections, we will focus on functional neurosurgical and interventional procedures in some neurological and behavioral disorders and discuss the future directions of this research.

Neuronal networks and the effects of electrical neurostimulation. The brain has a functional organization that can be represented as a collection of circuits. Many circuits are integrated to control certain functions. Some of these circuits are responsible for motor control, and others control sensory, memory, mood, endocrine, and autonomic functions. The recent advances in neurosciences and neuroimaging have allowed the identification of some brain circuits.[43,115-117] Motor function control by the cortico-striatal-pallidal-thalamic-cortical (CSPTC) circuits remain the main hypothesis and is supported by several animal model studies.[118] Defects in certain parts of this circuit produce movement disorders such as PD. Both direct and indirect pathways are organized within the basal ganglia circuit (**Figure 1**). The direct pathway fibers project from the putamen and pass monosynaptically through the basal ganglia output, the globus pallidus internus (GPi), and the substantia nigra (SNr), whereas the indirect pathway fibers project multisynaptically through the globus pallidus externa (GPe) and subthalamic nucleus (STN) and terminate at the GPi and SNr. Fibers from both pathways project to the thalamus and therefore to the frontal cortex at the precentral motor cortex, which sends projecting fibers to the basal ganglia to close the circuit loop. It was suggested that the direct pathway regulates movement initiation while the indirect pathway works as a switch from one action to another during movement. In these pathways, gamma-aminobutyric acid (GABA) is dominant in most fiber projections within the deep subcortical structures,

Table 1 - Functional neurosurgery selected clinical applications.

| Clinical disorders	Functional surgical procedures
Movement disorders	Deep brain stimulation and neuroablation
Epilepsy	Resective, disconnective and neuromodulation procedures
Pain	Neuroablative procedures and neuromodulation
Psychiatric disorders	Neuroablative and neuromodulation surgeries
Addiction	Neuromodulation surgery
Brain tumors and lesions	Stereotactic biopsy procedures
Motor function disorders (for example, quadriplegia)	Brain machine interface
Visual and hearing loss	Artificial prosthesis implantation
Memory disorders	Neuromodulation
Cognitive and consciousness disorders	Neuromodulation
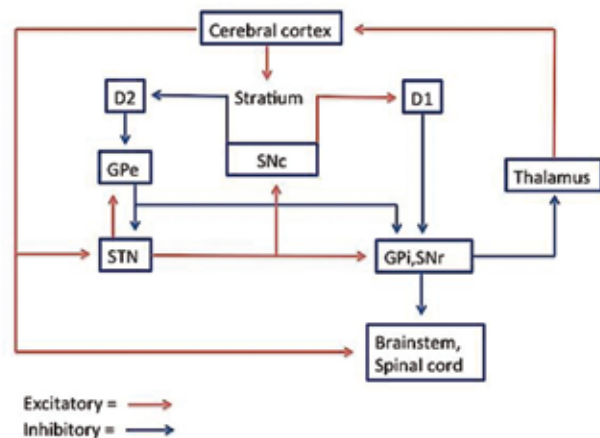
Figure 1 - Simplified diagram of the basal ganglia motor circuitry in normal state. SNc - substantia nigra pars compacta, GPe - globus pallidus externus, STN - subthalamic nucleus, GPi - globus pallidus internus, SNr - substantia nigra reticulate

where it regulates inhibitory mechanisms. The cortico-basal ganglia and thalamocortical projections are glutamatergic and regulate excitation. Within the deep subcortical structures, the fibers passing from the STN to the GPi and SNr are the only glutamatergic projections. Dopaminergic projections to the striatum reduce basal ganglia output, which in turn increases the activity of the thalamocortical projections. There are 2 types of dopamine receptors: inhibitory (D1) and excitatory (D2) receptors. Therefore, dopamine can serve as either an inhibitory or excitatory signal depending on the type of receptor.[119]

Functional neurosurgical procedures for movement disorders target certain sites in the CSPTC circuits. These procedures include ablation, neurostimulation, gene therapy, cell transplantation, and optogenetics. Similar to movement disorders, other neurological and psychiatric disorders might be caused by dysfunction in certain parts of a network that connect various regions of the brain. Surgical intervention in a component of any disorder-specific network can alter the clinical features of the disorder at a therapeutic level. Deep brain stimulation involves the delivery of a reversible and adjustable electrical volume into a specific deeply located neuronal tissue. In contrast, stereotactic lesioning or ablation destroys neuronal tissue in a given network. Despite the extensive clinical use of DBS, the mechanism underlying its efficacy remains unclear.[120] The effects of high-frequency electrical stimulation are similar to those of a lesion, thereby enabling this technique to exert an inhibitory effect on the neural network by inhibiting membrane action potentials or by blocking neurotransmission in the STN.[121] The DBS can also increase the release of neurotransmitters such as glutamate in the STN and dopamine in the GPi.[122] In general, the most robust hypothesis postulates that DBS serves as a regulatory mechanism by inhibiting neurons and activating axons in motor circuits.[123,124] The same hypothesis might be applied for other disorders like epilepsy, psychiatric disorders, and chronic pain. In epilepsy, the electrical stimulation of certain neuronal targets can modulate epileptic activities.[113] This antiepileptic modulatory effect might be related to a release of inhibitory neurotransmitters or to direct neuronal inhibition that can induce sodium channel failure and block depolarization.[98] In pain therapy, electric stimulation either exerts therapeutic effects by releasing opioids, as suggested by some investigators, or modulates several descending systems to reduce pain.[125,126] However, the effect of electric stimulation on pain is site-dependent. The effect of DBS or ablative procedures on psychiatric disorders was suggested to be based on the modulation of certain frontal lobe circuits.[127] These circuits can be divided into several

groups: dorsolateral circuits that project from the dorsolateral frontal lobe to the caudate head and medial putamen, orbitofrontal circuits that project from the inferolateral prefrontal cortex to the caudate and nucleus accumbens, and an anterior cingulate circuit that originates from the anterior cingulate and extends to the ventromedial striatum.[127] Despite several hypotheses that might explain the mechanism of neurostimulation, the exact effect of neurostimulation remains unknown. However, neurostimulation remains a potent therapy for many functional neurological disorders.

Stereotactic DBS implantation and lesioning surgery. In this section, we will discuss the common targets of movement disorder surgery as an example of a stereotactic surgical procedure. Stereotaxy is defined as the location of points within the brain using an external, 3-dimensional frame of reference based on the Cartesian coordinate system. Stereotactic surgery is based on the identification of internal anatomical landmarks. The anterior (AC) and posterior (PC) commissure are the usual internal landmarks that can be identified by reference to an X, Y, and Z coordinate system provided by a stereotactic frame fixed on the patient's head (**Figure 2b**). With respect to the AC-PC distance and mid-commissural point (MCP), anatomical targets such as the STN, GPi, and ventralis intermedius (VIM) can be localized indirectly. The X, Y, and Z coordinates of these targets are calculated with respect to the intercommissural plane (IC) and MCP. If the target cannot be localized with respect to the MCP, direct visual identification or other internal anatomical landmarks may be used, for example, in cases where the subcallosal cingulate gyrus (including Brodmann area 25) is targeted to treat depression. The procedure usually starts with frame placement on the skull. Different groups use various types of frames. In our institution, we use a Leksell series G frame (©Elekta Instrument AB, Stockholm, Sweden). It is important to avoid misalignment of the frame during placement. Frame placement is facilitated by the use of earplugs that can help minimize lateral tilt (roll) or rotation (yaw). The anteroposterior axis of the frame is angled such that it is parallel to the AC-PC axis, generally using an external landmark like a line drawn between the inferior orbital rim and external auditory canal, which is approximately parallel to the AC-PC plane.[128] Next, the frame is fixed to the skull using pins under local anesthesia, sometimes in addition to intravenous sedation. If earplugs are used to facilitate frame placement, they should be carefully removed prior to tightening the frame pins to minimize pain in the external ear canal. A MRI or CT localizer is applied on the frame (**Figure 2a**). Many centers use MRI to identify the AC-PC and other internal anatomical landmarks for targeting. Some centers fuse
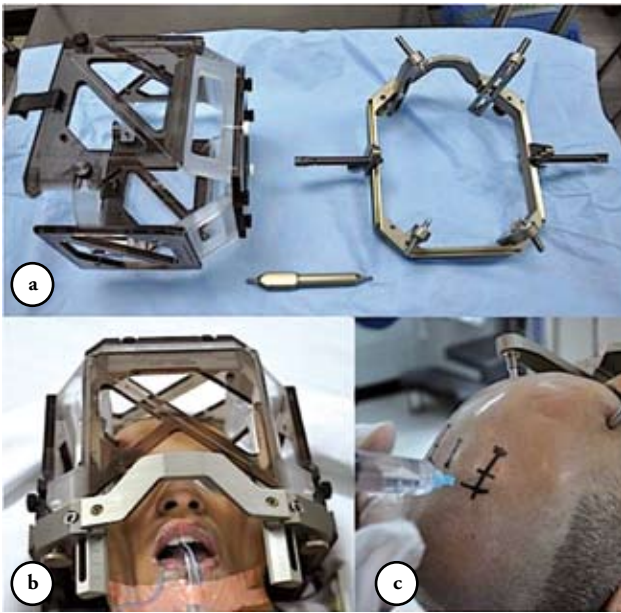
Figure 2 - Intraoperative photographs depicting: **a)** demonstrating the Leksell frame (right) and MRI localizer (left). **b)** Leksell frame and MRI localizer applied on the patients head. **c)** Local anesthesia infiltration at the marked skin opening site.
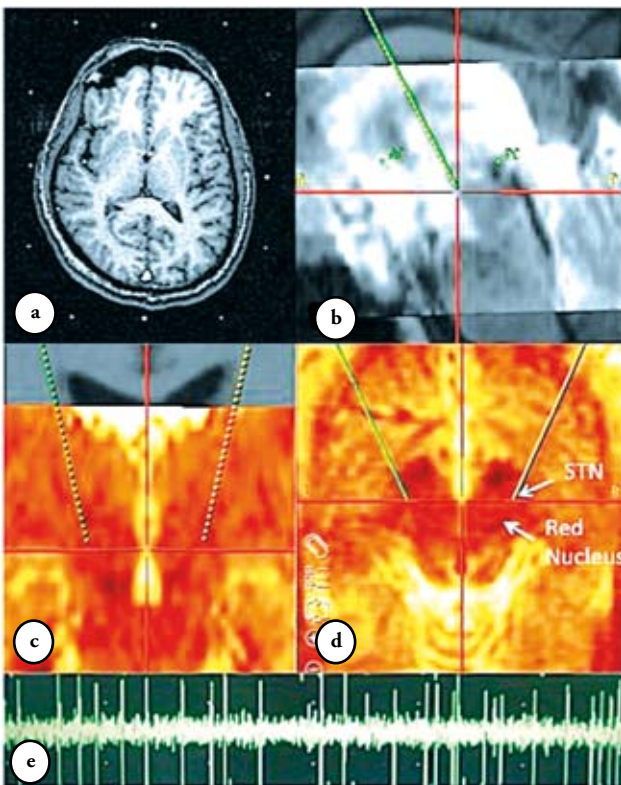
Figure 3 - MRI based stereotactic STN targeting showing: **a)** An MRI obtained with the Leksell frame showing the localizer markers. **b)** Demonstrates the relationship between the tentative STN stereotactic target and AC-PC plane using StealthStation® planning station (Medtronic Inc., Minneapolis, MN, USA). **c)** Trajectory planned to avoid ventricle. **d)** Planned STN tentative location in relation to red nucleus. **e)** STN microelectrode recording firing characteristics. STN - subthalamic nucleus

CT scans obtained with the frame with the preoperative MRI. Ventriculography was used in the past, but was eventually replaced by CT and MRI.[124] Surgical planning software is helpful to correct misalignments of the frame, identify a cortical entry point that will avoid the sulci and ventricle, and aid in target localization (**Figures 3a-d**). This software is used as an adjunct to the frame-based stereotactic method, and some programs can fuse patient images and even apply a deformable brain atlas to the images. Many centers use MRI for stereotactic targeting. T1-weighted, volumetric imaging of the whole brain, inversion recovery, and T2-weighted axial sequences are the most commonly used in practice. The MRI with gadolinium as a contrast agent is useful to delineate the cortical and subcortical vessels so these structures can be avoided during electrode entry and trajectory. **Table 2** summarizes the X, Y, and Z stereotactic anatomic coordinates of selected targets. The STN can be targeted based on the red nucleus (RN); the STN is located 3 mm lateral to the lateral RN border (x coordinate), and the anterior RN border serves as the y coordinate. The z coordinate is 2 mm below the upper RN border.[129] Several authors have used other methods to refine image-based targeting because AC-PC coordinate-based targeting is not always sufficient to accurately locate the STN and other targets.[124] In general, the overall accuracy of frame-based stereotactic targeting using CT is approximately 1.5 mm.[130]

Most surgeries are performed under local anesthesia, although in certain cases such as pediatric and some dystonia cases general anesthesia is used. Local

Table 2 - Commonly used stereotactic coordinates of selected targets for DBS.

| Target	X	Y	Z
STN	11-13 mm lateral to midline	3-4 mm posterior to MCP	4-5 mm below AC-PC plane
GPi	19-21 mm lateral to midline	2-3 mm anterior to MCP	4-5 mm below AC-PC plane
Vim	11-12 mm lateral to the third ventricular wall	6-7 mm posterior to MCP	At AC-PC plane
Vc	12-13 mm from midline for facial pain, 14-15 mm for upper limb pain, 16-17 mm for lower limb pain	2-3 mm anterior to PC	At AC-PC plane
PVG	2 mm lateral to the medial third ventricle wall	2-3 mm anterior to PC	At the level of AC-PC plane
AN	6 mm lateral to MCP	8 mm anterior to PC	12 mm above AC-PC plane

STN - subthalamic nucleus, GPi - globus pallidus internus, Vim - Ventralis intermedius, Vc - ventralis caudalis, PVG - periventricular gray, AN - anterior thalamic, PC - posterior commissure, MCP - mid commissural point, AC - anterior commissure

anesthesia allows the optimal neurophysiological exploration of some targets, such as the STN and VIM. In addition, it allows the assessment of intraoperative clinical response to stimulation. In the case of PD, anti-Parkinsonian medications are usually discontinued the night before surgery to allow better assessment of the clinical response to intraoperative stimulation. During the procedure, the Leksell frame base is attached to the operating table. The skin opening is typically anterior to the coronal suture and lateral to the midline by at least 2 cm and is made after the skin has been infiltrated with local anesthesia. A burr hole is placed either at the planned cortical entry point or in a standard location (one cm anterior to the coronal suture and 2 cm lateral to the midline). All targets are initially localized using a stereotactic anatomic method. Neurophysiological verification is useful to refine the final position of the DBS lead or lesion. This neurophysiological monitoring includes microelectrode recording (MER), semi-MER, and macrostimulation. While MER is deemed essential by many groups,[124] other groups argue that MER is not necessary in functional stereotactic neurosurgery.[131,132] Nevertheless, there are limitations to pure anatomical targeting such as stereotactic system accuracy, intraoperative brain shift, image distortion, and poor visualization of the target. We prefer to utilize MER with the patient awake in the majority of cases, followed by DBS lead stimulation as the final step. In 3 cases, we used dexmedetomidine (Precedex) for sedation, which did not affect MER, although we noticed more pulse artifacts during 2 of these procedures (unpublished data). The most common MER method involves the recording of a single unit using high-impedance (0.2-0.6 mohm) microelectrodes. Electrodes are typically made of tungsten or platinum-iridium and are approved by the United States FDA. Each target has a special firing rate and pattern in addition to the specific firing pattern of the audible noise. In general, MER allows the mapping of the target borders and anatomical boundaries. A detailed knowledge of each target and its surrounding anatomy is crucial. As an example, MER for STN targeting starts 10 mm above the STN and usually begins with a recording of thalamic nuclei firing. The thalamic nuclei (nucleus reticularis [Rt], ventralis oralis anterior and posterior [Voa and Vop]) are characterized by a slow firing rate (bursting cells firing at a rate around 15 Hz and irregular tonic firing at around 28 Hz). Below the thalamus are the zona incerta (ZI) and the fields of Forel, which are characterized by a decrease in background activity; some bursting cells can be found in this area. Entry into the STN is indicated by an increase in background noise and firing rate with high-amplitude, irregular spikes (**Figure 3e**). The dorsolateral STN neurons respond to passive and active limb movements; tremor cells can be identified as well. The STN exit is indicated by the absence of background activity. The distance between the lower border of the STN and the upper border of the SNr is usually less than 3 mm. The SNr fires at a rate of 50-70 Hz with a more regular pattern. Microstimulation of the recording electrode can induce the inhibition of SNr activities, which is not true of the STN.[133] The final DBS distal electrode contact is usually placed at the lower end of the STN or upper end of the SNr.

The MER during GPi targeting is used to identify the globus pallidus externus (GPe) and GPi. After passing the GPi, the optic tract is identified. Stimulation at low intensity can evoke phosphenes, flashing lights in the contralateral visual field. The GPi usually fires in high-frequency discharges, typically around 60-90 Hz. The GPi firing rate in dystonic patients may be lower than that in patients with PD.[134] The sensorimotor neurons of the GPi can be either inhibited or excited by limb and orofacial movements. Tremor cells can be identified on some occasions. The internal capsule can be encountered medial or posterior to the GPi. The final DBS distal contact is placed one mm above the optic tract and 3 mm anterior to the internal capsule. Incases of pallidotomy, the lesion is usually placed 2 mm above the optic tract. The MER for Vim is used to identify the motor and sensory thalamus. The sensory nucleus can be easily identified during MER due to its somatotopic representation. Tactile stimulation can evoke responses from sensory nucleus neurons. Therefore, neurons that respond to movements (kinesthetic responses) can be identified. Tremor cells may be recorded, and the stimulation of these cells usually induces tremor reduction or arrest. The DBS electrode is placed 3 mm anterior to the sensory nucleus and Vim border, which is the same location that is targeted for lesioning.

Macrostimulation is an important step that precedes DBS electrode implantation. The most commonly used electrodes have 4 contacts, each with a diameter of 1.27 mm and a height of 1.5 mm. Two common models are based on contact separation: the 3389 model that has an intercontact distance of 0.5 mm, and the 3387 model that has an intercontact distance of 1.5 mm (Medtronic, Minneapolis, MN, USA). Other manufacturers have designed a 4-contact electrode with similar contact spacing. These electrodes feature "active tip" technology and a diameter of 1.4 mm (St. Jude Medical Inc, St. Paul, MN, USA) (**Figure 4**). In general, the DBS electrode is implanted with the guidance of a fluoroscope to verify its location and to rule out any deviation (**Figure 4**). Microlesional effects can induce improvement in tremor and PD rigidity and bradykinesia, but this is rarely seen in cases of dystonia. The DBS electrode is stimulated using an external stimulator, and the same stimulation
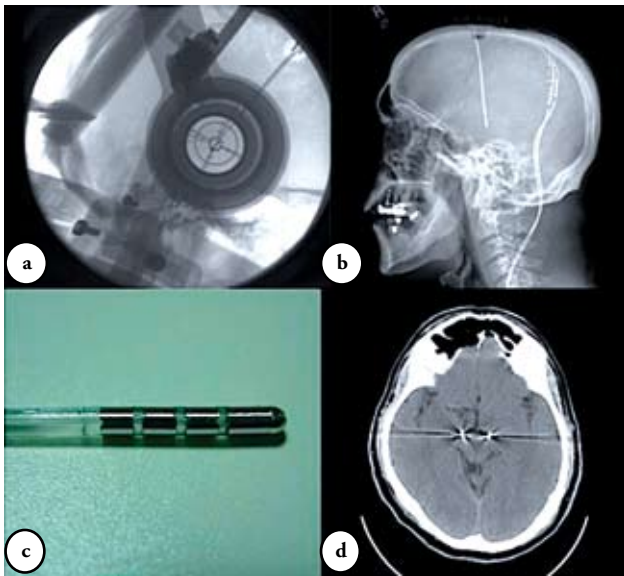
Figure 4 - Radiographs and photographs showing: **a)** Fluoroscopy localization of DBS electrode implantation. **b)** X-ray lateral view post implantation of bilateral STN-DBS electrodes. **c)** Demonstrates DBS electrode with "active tip" technology from St Jude medical (St. Jude Medical, Inc., St Paul, MN, USA). **d)** Computerized tomography demonstrating bilateral STN DBS electrodes. DBS - deep brain stimulation, STN - subthalamic nucleus

Table 3 - Correlation between stimulation induced clinical effects and the likely electrode sites in selected DBS targets.

Target	Electrode sites	Stimulation induced clinical effects
STN	Posteriorly or medially located electrode	Persistent paresthesia at low amplitude (stimulation spread to medial lemniscus
	Lateral or anteriorly located electrode	Tonic contraction and dysarthria at low stimulation amplitude (internal capsule stimulation effect)
	Medial and anteriorly located electrode	Diplopia (oculomotor effect)
	Potentially too deep or medial electrode location	Adverse effect on mood
	Electrode location is above or too anterior to the STN	Absence of adverse effect and benefit
	STN location	Dyskinesia
Vim	Posteriorly located electrode	Persistent paresthesia at low amplitude
	Laterally located electrode	Dysarthria or tonic contraction (internal capsule stimulation effect)
	Electrode location is above or too anterior to the Vim	Absence of adverse effect and benefit
GPi	Deep location	Visual response (namely, phoshenes) (stimulation spread to optic tract)
	Posterior or medially located electrode	Dysarthria or tonic contraction (internal capsule stimulation effect)
	Electrode location is above or too anterior or lateral to the GPi	Absence of adverse effect and benefit

STN - subthalamic nucleus, Vim - ventral intermediate,
GPi - globus pallidus internus, DBS - deep brain stimulation
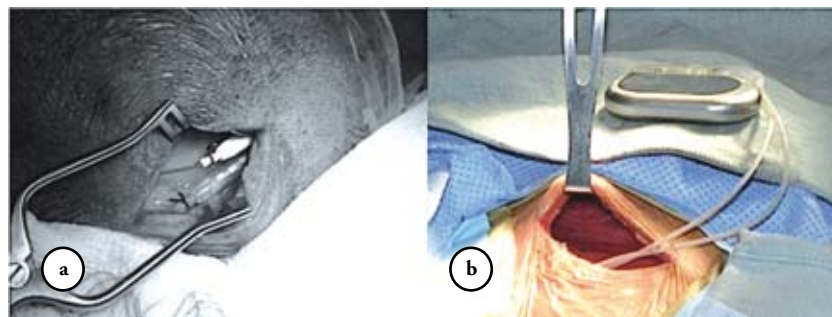
Figure 5 - Intraoperative photograph showing: **a)** Parietal skin opening for connecting DBS electrodes with the extension leads. The right side is covered with a white radiopaque sleeve. **b)** Subpectoralis fascia created pocket for internal pulse generator implantation. DBS - deep brain stimulation

parameters used in clinical settings (frequency of 130 Hz, pulse width of 90ms, and amplitude of 1-5 V). The common clinical effects that occur following macrostimulation or chronic DBS stimulation in various locations are summarized in **Table 3**. After the DBS electrodes are implanted, the internal pulse generator (IPG) and its extension leads can be implanted during either the same procedure or a subsequent procedure (**Figure 5**). This is carried out under general anesthesia with the patient in the supine position with his/her head turned contralaterally. The IPG is usually placed in the infraclavicular area, approximately 2 cm below the clavicle and 3 cm from the lateral manubrial border. Depending on the thickness of the skin and subcutaneous tissue, the IPG is placed either subcutaneously or under the pectoralis muscle fascia (**Figure 5**). In the case of lesioning, stimulation is performed using the radiofrequency lesioning electrode while watching for side effects or benefits. This is followed by increasing the temperature of the electrode tip to 45°C to test for any adverse events; any temperature above 45°C can cause permanent tissue damage. Then, the lesion is induced by steadily increasing the temperature from 60 to 90°C over 60 seconds. The lesion can be shaped according to the target volume by applying multiple lesions.

There is significant variability in DBS surgical techniques and approaches related to surgeon preference as well as the surgical system and instrument settings.

There is no consensus regarding the best surgical approach for DBS due to the lack of randomized studies comparing these approaches. Complications from the DBS procedure include infection, which has been reported to occur in 1-15% of cases in several reports.[124] However, most studies report an infection rate of less than 5%. The most common site of infection is the IPG site. Antibiotic treatment may be sufficient when the infection is superficial. In many cases of IPG infection, the removal of the IPG and extension leads is sufficient to treat the infection, and the intracranial DBS lead does not need to be removed. There is only one case report of DBS infection-related brain abscess.[135] Intracranial hemorrhage occurs in around 3.4% of DBS cases, in contrast to 15.8% of lesioning cases.[136] However, some reports indicate no difference between bleeding rates in lesioning and DBS procedures.[137] Hypertension was found to be a risk factor for intracranial bleeding during this procedure.[138] The risk of GPi hemorrhage was found to be greater than that of STN hemorrhage (9.8 and 2.9%).[139] Hardware-related complications include lead migration, DBS lead fracture, skin erosion, pain at the IPG site, and malfunction of the IPG. Other complications may be induced by stimulation such as speech disturbance, balance problems, ocular symptoms, and the internal capsule stimulation effect. These can usually be reversed by adjusting the DBS program. Dyskinesia is usually a self-limiting adverse effect and suggests a good placement of the DBS lead. If a significant adverse stimulation effect limits the benefits of DBS, the location of the lead should be verified and adjusted accordingly. Adverse neuropsychiatric effects can occur after implantation and before chronic stimulation. These include a state of confusion after STN DBS, which is usually transient.[139] Other neuropsychiatric disorders include hypomania, which was reported to occur in 4-15% of patients, and depression, which was found in 1.5-25% of patients.[124] These adverse effects are usually resolved after DBS program adjustment. Other complications include seizure, which was reported to occur in 3.1% of cases.[140]

Clinical applications of functional neurosurgery. In this section, we will examine the main indications for functional surgery in clinical practice. Each clinical disorder will be discussed briefly, and the main outcomes of surgical intervention will be explored. However, detailed discussions of disease pathophysiology are outside the scope of this review.

Movement disorders. The main targets of movement disorder treatment are the STN, GPi, and Vim. The main movement disorders treated are PD, dystonia, and essential tremor. Parkinson's disease affects 1-3% of all people over the age of 65 and is considered the second most common neurodegenerative disease. Despite medical therapy, 28% of PD patients suffer from disabling motor symptoms that include bradykinesia, rigidity, tremor, and gait instability. Fluctuation in motor symptoms usually indicates the failure of medical therapy to control PD symptoms. The selection process for DBS or lesioning therapy is a crucial step in PD management. The usual inclusion criteria include: 1) confirmed diagnosis of idiopathic PD; 2) significant PD symptoms with a severity of motor symptoms (while unmedicated) of >30/108 using the Unified Parkinson's Disease Rating Scale (UPDRS) part III; and 3) good motor symptom response to the levodopa challenge test, indicated by a >30% reduction in UPDRS part III scores. Overall, surgery controls symptoms of the extremities, in contrast to axial symptoms like speech, gait, and swallowing. The most common contraindications to surgery include dementia, concomitant medical problems that preclude safe surgery, extensive brain atrophy, and uncontrolled psychiatric disease.

Currently, the STN is the most frequent target of DBS to treat PD. A meta-analysis of the literature from 1993 to 2004 showed that the overall improvement in off-medication UPDRS part III scores after STN DBS was around 52%.[141] Levodopa dose reduction was between 50-60%, which should lead to improvement in levodopa-induced dyskinesia.[142] Many authors have reported long-term sustained benefits of STN DBS.[124,142] The GPi DBS also effectively controls PD symptoms, especially dyskinesia.[143] A randomized multicenter study showed no significant differences between STN and GPi DBS in controlling PD motor symptoms over 24 months.[144] The Vim DBS is limited to the treatment of PD. Tremor-predominant PD can be controlled by Vim DBS, but other symptoms like rigidity, bradykinesia, and dyskinesia are not alleviated. Pedunculopontine nucleus (PPN) DBS was found to decrease repeated falls in PD patients.[145] However, it does not control other symptoms. Combined STN and PPN stimulation did not improve overall motor scores.[145] Other groups benefitted from combined caudal zona incerta and PPN DBS to control axial symptoms in PD.[146] Overall, STN DBS remains the routine surgical therapy to treat PD symptoms in many centers worldwide.

The DBS therapy offers a therapeutic benefit for some patients with dystonia who are intractable to other treatment modalities such as medication and botulinum toxin injection. The DBS usually benefits patients with primary dystonia.[147] Patients with a DYT1 gene mutation respond better to DBS.[124] In contrast, secondary dystonia does not respond well to DBS.[124] The improvement in primary dystonia after bilateral GPi DBS was reported to be around 70% in one study.[148] Another multicenter report showed a 55% improvement in dystonia after one year of bilateral

GPi stimulation.[149] Cervical dystonia was found to improve by 60% at the 20-month follow-up.[150] The improvement in dystonia after DBS is delayed relative to improvements in PD and tremor. In addition to the aforementioned adverse effects of DBS, hypokinetic gait disorders with gait freezing can be induced by GPi DBS.[151] In a few reports, STN DBS resulted in dystonia improvement.[152] At present, the safety and effectiveness of bilateral GPi DBS in treating dystonia has limited the lesioning procedure to selected cases.

Different types of tremor such as essential tremor, cerebellar tremor, multiple sclerosis-related tremor, and tremor related to traumatic brain injury can be alleviated by Vim DBS. Tremor-predominant PD is also controlled by Vim DBS. In a series of 32 patients with essential tremor or PD-related tremor, 88% of the implanted electrodes induced significant tremor control.[124] Overall tremor improvement was found to be better following Vim DBS compared to lesioning (thalamotomy).[153] Multiple sclerosis distal tremor also responds to Vim DBS, and proximal tremor was found to respond better to zona incerta DBS.[154]

In 1997, Vim DBS received FDA approval for therapeutic use in the treatment of PD tremor and essential tremor. Subsequently, STN and GPi DBS were approved for PD in 2002. A Humanitarian Device exemption from the FDA was given to GPi and STN DBS for the treatment of dystonia. So far, more than 40,000 patients worldwide have received DBS therapy for movement disorders, mainly PD. Currently, there is strong evidence for the effectiveness of this therapy for movement disorders, which has created interest in its application to other clinical disorders.

Epilepsy. Resective and disconnective surgery to treat medically-resistant epilepsy has been well established over many years. However, many patients are not candidates for this kind of functional surgery or have failed to respond to resective surgery. Neuromodulation offers hope for these patients.[113] Neurostimulation of the peripheral or central nervous system has been proposed to treat epilepsy. This method has several potential advantages over resective surgery. For example, it is reversible and adjustable, multiple epileptic foci can be influenced by the stimulation of one target, and foci that cannot be safely removed can be stimulated. Several targets have been electrically stimulated, including the cerebellum, thalamus, subthalamus, hypothalamus, cortex, hippocampus, vagus nerve, and trigeminal nerve.[113] Recently, a pivotal multicenter, randomized, and blinded trial was conducted (SANTE, or Stimulation of the Anterior Nucleus of Thalamus for Epilepsy).[155] The patients in this study had medically intractable partial or secondarily generalized seizures and were not amenable to resective surgery. Data were collected from 110 patients in 17 US centers. All patients continued to receive antiepileptic medication during the trials. Within the first 3 months, only half of the patients received active stimulation. Thereafter, all patients were made "active" and were followed for a minimum of 13 months. During the blinded "on/off" evaluation, the reduction of seizure frequency was significantly greater in patients who received stimulation (40.4% versus 14.5%). At the long-term follow-up, 54% of patients had a ≥50% reduction in seizure frequency. Of the 81 patients who completed 2 years of follow-up, 13 had a ≥90% reduction in seizure frequency. A total of 13% of patients became seizure-free for at least 6 months. Among the patients in the study, 49 (44.5%) had undergone previous VNS implantation with no benefit.

Responsive neurostimulation (closed-loop) systems are currently undergoing an efficacy assessment.[156,157] These systems deliver stimulation in response to specific cues or commands detected by afferent sensors. The current results are promising; however, further investigation is needed to optimize detection algorithms and stimulation parameters. The FDA has approved vagus nerve stimulation for epilepsy treatment, and an FDA advisory panel recently recommended the approval of anterior thalamic stimulation. Other neuromodulation strategies under investigation include brain cooling, gene therapy, neuronal tissue transplant, transcranial magnetic stimulation, and drug delivery.

Pain. Several functional procedures have been employed to treat various medication-resistant pain disorders. These include neuroablative procedures such as dorsal root entry zone lesions, cordotomy, commissural myelotomy, hypophysectomy, and thalamotomy. In addition, facial pain remains a prime indication for neuroablative procedures. Several procedures have been employed for the treatment of other types of craniofacial pain and other pain disorders in the past. For example, the first functional neurosurgical procedure used to treat trigeminal neuralgia was open-surgery gasserian ganglionectomy, but this was subsequently replaced by percutaneous procedures and microvascular decompression.[158] More recently, stereotactic radiosurgery has been used to treat trigeminal neuralgia.[159] In general, the main indications for surgery are medically-resistant neuropathic pain or nociceptive pain. Currently, neuroablative procedures have been largely replaced by neuromodulation. The modulation of pain generation and transmission at different levels of the pain pathway is considered the major goal of current and new procedures. Neurostimulation has been used to treat pain for the last 4 decades.[1] The DBS targets for pain syndrome treatment include the sensory thalamus and periaqueductal (PAG) and periventricular

(PVG) grey matter.[160] The overall response rate to DBS is only around 50-60%.[1,160,161] So far, more than 1300 patients have received DBS for pain management.[162] Motor cortex stimulation for the treatment of refractory pain was pioneered by Tsubokawa et al.[163] This method was shown to be more effective for neuropathic facial pain than for other pain syndromes.[164] Spinal cord stimulation has also been used to control several neuropathic pain syndromes with sustained effectiveness.[165] In addition to neurostimulation, transcranial magnetic stimulation to treat pain is under investigation.[166] Radiosurgical hypophysectomy might also be useful to treat certain pain syndromes, especially cancer-related pain.[167] Drug delivery is another method of alleviating pain, and intrathecal drug delivery is the most commonly used method. This type of therapy is usually recommended for cancer pain.[168] Overall, several procedures can be employed for pain management. To date, neuromodulation is a major treatment strategy for different pain syndromes, although neuroablative procedures are still employed for certain pain disorders.

Psychiatric disorders. The history of psychosurgery is littered with controversy. In 1888, Burckhardt performed bilateral multiple resections of different lobes to treat psychiatric illness.[169] Subsequently, Moniz and Lima introduced the prefrontal leucotomy.[170] Freeman and Watts employed prefrontal lobotomy and transorbital lobotomy to treat different psychiatric illnesses.[171] Prior to the mid-1950s, around 20,000 lobotomy procedures were performed in the United States of America.[171] Due to the abuse of this procedure and the introduction of new psychiatric medications, surgery for psychiatric illness declined significantly. Since then, other neuroablative procedures have been introduced, including anterior cingulotomy, anterior capsulotomy, limbic leucotomy, and subcaudate tractotomy.[172] The success of DBS in movement disorders opened the door for other applications, including psychosurgery. Several trials have shown promising results. Anterior capsule stimulation for the treatment of obsessive-compulsive disorder was introduced in 1999. Subsequently, DBS of the subcallosal cingulate gyrus for the treatment of medically-resistant depression was employed in 2005.[173-175] Other targets for DBS include the nucleus accumbens, inferior thalamic peduncle, amygdala, septal area, habenula, and posteromedial hypothalamus. Vagus nerve stimulation is currently approved by the FDA to treat medically-resistant depression, but the clinical response has not been promising and may represent little more than a placebo effect.[176] Data from the most recent clinical trials support the efficacy of modern psychosurgery to control the symptoms of some psychiatric illnesses. The main aim of this surgery is to modulate the dysfunctional brain circuits that are responsible for the psychiatric disorder and restore their function.

Memory and cognitive disorders. Advances in neuroimaging have improved our understanding of memory and cognitive function. Dysfunction in memory circuits can be recognized using functional imaging methods such as positron emission tomography (PET) and functional MRI (fMRI). In 2008, the Lozano group from Toronto reported that DBS of the hypothalamus and fornix could modulate memory circuitry.[177] Subsequently, the same group conducted a clinical trial of bilateral fornix DBS in 6 patients with Alzheimer's disease.[178] The study was based on an open-label analysis of the clinical results over 12 months of continuous stimulation. They demonstrated some improvement on the Alzheimer's disease assessment scale and a slowing of the cognitive decline rate. Biological effects were investigated using PET scans, which demonstrated that stimulation was able to reverse glucose metabolism abnormalities. Moreover, the safety and reversibility of DBS were explored. Overall, this study paved the way for future clinical trials to compare DBS to medical therapy in a double-blind fashion. This type of therapy may be promising for millions of patients worldwide.

Other clinical applications of functional neurosurgery. Functional neurosurgery has been used to treat many disorders in addition to those described above. For example, cluster headache was successfully treated with ipsilateral posterior hypothalamus stimulation.[179,180] Deep brain stimulation has been used to treat addiction by stimulating the nucleus accumbens and was successful in controlling alcohol, nicotine, and heroin addiction.[181,182] The application of central thalamic DBS to improve cognitive function and consciousness in patients with a severe head injury and in a vegetative state showed that stimulation can promote functional recovery.[183,184] Phrenic nerve stimulation has been used to treat hypoventilation disorders in selected patients. It is estimated that more than 2500 diaphragmatic pacings have been performed worldwide.[185] Other applications of functional neurosurgery are found in the development of visual prosthesis[186] and brain-machine interfaces.[187]

Future directions. Functional neurosurgery is a progressive field in many respects. This field has been supported by advancements in many technologies and the development of neuroimaging techniques. Basic science research has also gained significantly from many functional surgical techniques that have been used to explore different areas within the brain. The path toward a better understanding and exploration of many brain circuits and functions has been paved by functional neurosurgery, and these techniques will remain at the forefront of future research.[1,188-191] In the

near future, the development of steering DBS electrodes will enhance programming processes and might improve clinical benefits by controlling the volume of tissue that is activated by electrical stimulation.[192] The current development of robotic surgery, frameless DBS implantation, and real-time MRI-guided surgery will enhance and facilitate many functional neurosurgical procedures.[193,194] Recently, a rechargeable IPG has overcome the need for repeated surgery for IPG replacement; manufacturers might someday be able to provide a small IPG that can be placed on the skull. Other advancements have been made in remote programming and monitoring systems that are able to interrogate and program the IPG through a special wireless network.

Optogenetics, which utilize light stimulation to interrogate brain circuits, will undoubtedly generate more discoveries in neuroscience.[195] Optical stimulation might replace electrical stimulation in the future, although many current limitations of this technology will need to be resolved. Advances in stereotactic radiosurgery might enable its clinical application to more neurological functional disorders (**Figure 6**).[196] High-intensity focused ultrasound gained more interest recently and was used recently in a clinical trial to treat functional disorders.[197] The stereotactic delivery of gene therapies or neuronal tissue transplants to treat a variety of neurological disorders have shown promising results that should motivate further research in this field.[198] At present, there is plenty of room for improvement in functional neurosurgery, and many new tools and applications are on the horizon.

In conclusion, the rapid growth of the field of functional neurosurgery has been enhanced and powered by advances in technology, structural and functional neuroimaging, and neuroscience. A better description of the pathological mechanisms of various neurological disorders will enable more precise interventions and a better understanding of the biological effects of various treatment modalities and therapeutic technologies.

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Figure 6 - Photo of Cyberknife machine at King Faisal Specialist Hospital & Research Centre, Riyadh, Kingdom of Saudi Arabia (CyberKnife®, Accuray Inc., Sunnyvale, CA, USA). Images used with permission from Accuray Incorporated.

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