Targeting in DBS

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Abbreviations

  DBS: deep brain stimulation    MRI: Magnetic Resonance Imaging
  CNS: central nerve system      PD: Parkinson disease
  Vim: ventralis intermedius nucleus  ET: essential tremor
  STN: subthalamic nucleus       FDA: Food and Drug Administration
  GPI: globus pallidus pars interna  TS: Tourette syndrome
  GPe: globus Pallidus pars externa  OCD: obsessive compulsive disorder
  SNr: substantia nigra reticulata  IPG: internal pulse generator
**WHAT IS DBS?**

DBS (deep brain stimulation) is a surgical treatment involving the implantation of brain pacemaker, which sends electrical impulses to target structure deep in the brain for controlling specific neural activity. The FDA approved DBS as a treatment for ET, PD and dystonia. DBS is also commonly used to treat chronic pain as well as depression.

**History of DBS**

The modulation of brain activity by direct electrical stimulation of the brain can be traced to 1870[ (1)]. It was shown that electrical stimulation of the motor cortex in dogs can elicit limb movement. Four years later, electrical stimulation was introduced as a tool for improving neurosurgical procedures in humans [ (2)]. The emergence and development of human stereotaxic devices provided neurosurgeons a chance to investigate the effects of stimulating deeper cortical structures [ (3)] as well as to identify these deeper structures by observing the effects of stimulation. Although stimulation had intraoperative use before 1960, its goal focused on delineating the ‘best’ target for a subsequent lesion.

In the early 1960s, high-frequency (100Hz) stimulation of the ventrolateral thalamus could diminish tremor [ (4)]. In the early 1970s, it is reported that chronic stimulation was used to therapeutically treat pain [ (5)], movement disorders, or epilepsy [ (6)]. It took decades of years to implement combining the implantable pacemaker technology with chronically implanted deep brain electrode for long-term chronic DBS [ (7)]. Since then, DBS has become increasingly used for treating a variety of disorders. The first widespread use of DBS in the US and Europe was for the treatment of ET or the tremor of PD. Also DBS has been reported for treating
dystonia involved the thalamus [(8)] and the GPi [(9)]. There have been a few recent reposts of DBS for TS [(10)] and OCD [(11)]. Furthermore, the advancements in neuroimaging, especially MRI and intraoperative electrophysiological recordings have increased stereotaxic surgical targeting accuracy.

**Hardware of DBS**

Figure 1 displays the major components of DBS hardware: the implanted pulse generator (IPG), extension and lead (also called electrode). The IPG is a battery-power neurostimulator encased in a titanium housing, which sends electrical pulses to the brain interfere with neural activity at the target sites. DBS leads are 4 thin coiled wires insulated in polyurethane. Each wire ends in a 1.5mm platinum iridium electrode, resulting in 4 electrodes ending at the tip of the lead. These quadripolar leads is implanted in the brain with the electrodes positioning at the target cerebral sites and thus they deliver stimulation using either one electrode or a combination of electrodes. IPG and lead are connected by extension, an insulated wire that runs from the head, down the side of the neck, behind the ear to the IPG, which is placed subcutaneously below the clavicle or abdomen. The stretch coil extension is 15% extensible, which accommodates the natural movement of the head, neck and shoulders.
All the hardware of DBS is surgically implanted inside the body. Under local anesthesia, a hole about 14mm in diameter is drilled in the skull and the electrode is inserted, with feedback from the patient for optimal placement. The placement of the IPG and lead then occurs under general anesthesia.

**Surgical Procedure of DBS**

The surgical procedure of DBS is similar to the ablative stereotactic neurosurgery, except the final stage of electrode implantation.

First, a stereotactic head frame is fixed to the skull to establish a 3D coordinate system to allow correlation of the preoperative imaging with each point in the brain and to prevent intraoperative head movement. Holloway and colleagues [(12)] proposed frameless stereotaxy using bone fiducial markers to improve patient comfort. Thereafter CT and/or MRI scanning are performed to identify the anterior and posterior commissures (also ventriculography). The target sites of DBS may be or may not be directly indentified in the CT and/or MRI image due to the limit of resolution, therefore, direct or indirect targeting methods depending on imaging process help to locate the target structure in patient’s brain.

Microelectrode recording (MER) and microstimulation and/or macrostimulation is performed to determine the best possible location for the DBS electrodes: optimal benefit and a large therapeutic window between beneficial and adverse effects. After the optimal location for implantation of the electrode has been decided, the DBS lead (macroelectrode) is secured to the skull with a plastic cap, metal plate, or cement. The IPG can be implanted the same day.
Stimulation settings are adjusted by means of a programmer placed on the skin overlying the IPG. The adjustable stimulation parameters include frequency (0-185Hz), pulse width (60-450sµ), voltage (0-10.5V), and stimulating contacts (monopolar or bipolar stimulation).

Fig. 2. Surgical procedure of DBS in MRI [(36)].

**Mechanisms of DBS**

Although the application of DBS has a long history, the therapeutic mechanism of DBS is currently incompletely understood. In addition, no single mechanism has emerged to account for the effect of DBS in different brain regions and in different diseases. The effects of DBS have been well documented to be frequency dependent, with the greatest relief of symptoms at >100 Hz and no therapeutic relief at <50 Hz. Stimulation pulse width (duration) determines which neural elements are preferentially affected; longer pulse widths (1-10ms) influence the cell soma, whereas shorter pulse widths (30-200µs) mainly affect axons. Furthermore, DBS
results in highly localized stimulation because relatively low currents are used which result in small current spread (about 2-3 mm with an intensity of 2mA) and the intensity of stimulation decreases proportionally to the square of the distance.

The general therapeutic stimulation parameters of DBS have been derived primarily by trial and error, from the almost immediate effects on, such as tremor, rigidity, bradykinesia, paresthesia and chronic pain in patients during surgery. The exact DBS parameters, including the stimulus amplitude, duration and frequency band, vary with the treatment and with the targeted brain region. At present, with most commercially available stimulators, these parameters can be externally changed and fine-tuned over time. However, DBS allows only open-loop continuous stimulation, which does not take into account the continuous neural feedback from the individual patient.

It is suggested that the mechanism is reversible inhibition of the target site since the results and effects are comparable to ablation. Several studies proposed that high-frequency stimulation increases the excitatory response from the implanted site [ (13)]. GPi stimulation may result in activation of GPe GABAergic axons [ (14)] that inhibit GPi neurons. A similar phenomenon may exist with STN DBS. Two additional hypotheses have been proposed as the mechanisms of DBS: (1) depolarization blockade of myelinated axons; (2) ‘neuronal jamming’ whereby activation of fibers transfers non-physiological and incomprehensible messages to
downstream target nuclei, which are then disregarded. It is likely that the neuroanatomical of various effects of DBS are complex incorporating a combination of various mechanisms (See the above table: How does DBS work?[15]).

**DBS vs. ablation**

There are two surgical-based techniques to benefit the affective disorder diseases we mentioned above: ablation (thalamotomy and pallidotomy) techniques and DBS. DBS appears to have the same effect as ablation-blocking neuronal transmission in the target nucleus to improve of tremor and Parkinsonism. However, DBS electrode implantation causes fewer permanent neurologic adverse effects compared with ablation because much less brain tissue is destroyed [16]. Radiofrequency ablations may be inadvertently expanded or be misplaced to involve important structures close to the intended target, which potentially cause permanent damage of tissue and loss of function. With DBS, stimulation parameters can be finely adjusted to maximize beneficial results and minimize adverse effects caused by mild current spread to adjacent structures. DBS electrodes can also be surgically repositioned if they are placed suboptimally at the first time. Compare to the controllability of DBS, the effects of ablation are irreversible and unchangeable without additional surgery.

Ablation is usually performed with the patient awake; however, DBS requires an additional urgery performed under general anesthesia to implant the IPG and extension wire. Also, IPG needs to be replaced by surgery every 2 to 7 years due to the battery out of

![Fig. 3. Complications of DBS in MRI. Left: Hemorrhagic cortical event. Right: Ischemia](image)
power. Approximately 25% to 30% of patients with DBS experience hardware complication \[(17)\], typically mechanical hardware breakage or skin erosion over the hardware, which usually require replacement of damaged or infected hardware and treatment with antibiotics. In patients with severe postural instability and frequent falls, ablative surgery may be preferred since falls may damage or displace DBS hardware. In addition, DBS is much more expensive procedure compared than ablation; thus in many regions of the world, ablation is the only affordable surgical option when medication is not effective to the progress of the disease.

**WHAT ARE THE TARGETS IN DBS?**

The most popular target sites for DBS are the vertralis intermedius nucleus of the thalamus (Vim), the subthalamic nucleus (STN), and the globus pallidus pars interna (GPi).

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**Fig.4.** Targets in DBS. Left: describes the inhibitory and/or excitatory relationship among the targets in DBS. Right: shows the anatomical location of targets in hand-drawn picture \[(35)\].
Ventral Thalamic Nuclei

The cerebellar afferent receiving zone of thalamus (human VIM nucleus) has been the primary target for the treatment of tremor. These nuclei receive excitatory glutamatergic afferents from the deep cerebellar nuclei, excitatory glutamatergic afferents from the cerebral cortex, and inhibitory GABAergic inputs from the reticular nucleus of the thalamus. The output from these nuclei primarily targets motor areas of cerebral cortex but has also been shown to project to striatum. Thus, although Vim is commonly viewed as a simple relay for information from the cerebellum to cerebral cortex, the synaptic connections are complex and DBS likely influences multiple elements.

Anatomically, Vim is a complexly connected structure locating in the ventrobasal thalamus. Dorsally, Vim is bordered by the dorsal region of the ventral tier nuclei. Posterior to the Vim lies the principal sensory nucleus ventral caudalis (Vc) or ventral posterior lateral nucleus (VPL). Anterior to the cerebellar receiving area lies the region that receives afferents from the basal ganglia (GPi, SNr), incorporating ventro-oralis anterior (Voa), ventral anterior nucleus (VA). The medial border of Vim is with Vim.i, which is anatomically similar to Vim but receives proprioceptive afferents with receptive fields in the face region. Laterally, Vim is bordered by the posterior limb of the internal capsule. Organization within Vim is strictly somatotopic, with face followed by hand followed by leg from medial to lateral.

Subthalamic Nucleus

The STN has become the most commonly used target for DBS in the treatment of PD. The STN is an important node in basal ganglia circuits, serving as major target for cortical afferents and
also receiving multiple inputs from other basal ganglia components. The STN receives glutamatergic excitatory afferents from the frontal lobe of the cerebral cortex, GABAergic inhibitory afferents from the GPe, and excitatory afferents from the parafascicular nucleus of the thalamus. The output from the STN is glutamatergic and excitatory to both segments of the globus, to the substantia nigra pars reticulata (SNr), and to the pedunculopontine area. Thus the DBS in the STN has the potential to influence a variety of afferent and efferent targets and may have different effects on different neurons.

Anatomically, the STN is a complex, biconvex lens-shaped, triply oblique structure. Its maximal length is 13.2 mm rostrocaudally and 8 to 9 mm mediolaterally. STN is bordered on its anterior and lateral sides by the corticobulbospinal tract, while posteromedially lies the prelemniscal radiation and the red nucleus. The dorsal border of STN is with the lenticular fasciculus anteriorly, the thalamic fasciculus posteriorly, with the thalamus dorsal to the latter. The ventral border is formed by substantia nigra reticulate (SNr). STN is organized into motor, limbic, and associative regions. In the axial plane, the STN slopes form anteromedial to posterolateral, parallel to the cerebral peduncle below. Whereas the limbic region lies in the anteromedial portion, the sensorimotor region of STN lies in the posterolateral portion, and within this area it lies dorsally. Some mapping strategies are directed toward locating the motor region by confirming the presence of movement evoked neural responses.

**Globus Pallidus pars interna**

The GPi is another commonly used DBS target for the treatment of PD and meanwhile is increasingly targeted for DBS treatment of dystonia. The GPi labeled in figure 4 is one of the
primary output nuclei of the basal ganglia and the main output representation of limb movements [Mink 1996]. The GPi receives excitatory glutamatergic afferents from the STN, inhibitory GABAergic afferents form striatum, inhibitory inputs from the GPe, and nigral dopamine afferents. Due to the size and geometry, the effect of stimulation in the GPi is more likely to restrict to the nucleus, but the potential remains for the possible spread to adjacent structures and pathways, especially the GPe.

Anatomically, GPi is the internal segment of globus pallidus (GP) and the motor region of the GPi is the target for DBS in PD and dystonia. The GPe forms the lateral border of GPi, and medially, the dorsal border. The posterior limb of internal capsule forms the posteromedial border. The ansa lenticularis, the main outflow of GPi, lies below GPi coursing medially and anteriorly. Below this white matter lies the optic tract coursing posterolaterally toward the lateral geniculate nucleus. GPi is separated from GPe by the internal medullary lamina.

**HOW TO TARGETING IN DBS?**

Given the small size of DBS targets, targeting is a critical step in the DBS surgical procedure. Accurate preoperative targeting influences directly and significantly the operating time and most importantly, the outcome of the surgery. There are directly or indirectly methods performed preoperatively or intraoperatively.
By brain atlas

The targeting based on a standardized brain atlas is also called ‘indirect targeting’, a common procedure used for DBS targeting purposes mainly when the targets of DBS is not clearly visible in MR T2-weighted images. 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. Registering 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 registration uses the midcommissural point (MCP) or the PC as reference, which is calculated after selecting the AC and PC coordinates (Fig.5). 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. Coordinates for the sensorimotor GPi are selected as 19 to 21 mm lateral to the midline, 2 to 3 mm anterior to the MCP, and 4 to 5 mm ventral to intercommissural plane. The Vim is targeted 11 to 12 mm lateral to the
wall of the III ventricle, at the level of the intercommissural plane. Most commonly, the goal is to target the topography of the upper extremity, which carries the greatest impact for quality of life. In terms of anterior-posterior position, the Vim is typically located between 2/12 and 3/12 of the AC-PC distance rostral to the posterior commissure. These coordinates may not represent the ideal location for implantation but are used as initial anatomical targets, which are verified by physiological recordings. Figure 6 demonstrates a typical digitized version of the Schaltenbrand and Wahren atlas registered to the MRI space to conform to the patient’s anatomical structures. These atlas-and-registration-based targets are than cross-correlated with the direct visualization target.

Since the scanning performed in a 3D space, when oblique slices produced by scanner, 2D registration is not qualified to register atlas to MRI slice by slice. 3D atlas-based targeting may overcome this difficulty. Briefly, 3D surfaces (fig. 7 left) representing visible subcortical nuclei were segmented from a high-resolution MRI. These surfaces were then aligned with 2D Schaltenbrand and Wahren slices [8] to define outlines of nonvisible nuclei such as STN and lofted to create the additional 3D surfaces.

Atlas-based 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 deformable 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.

Regarding the registration methods, it is roughly divided into rigid and non-rigid algorithm according to the characteristic of deformation from source image to reference image. Rigid registration is referred as primarily affine transformation of source image involving translation, rotation as well as scaling. Rigid registration is also used as a pre-alignment step for non-rigid transformation. Non-rigid registration includes intensity-based algorithm (demons/ B-spline/thin-plate-splin/ adaptive bases algorithm [(18)]) and segmentation-based registration. Mutual information [(19)] is the most commonly used standard for automatically measure the goodness of the registration result. More details will be skipped in this paper.

**By visible surrounding anatomical landmarks**

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 read nucleus can be used as landmark for the anteroposterior localization of the STN target [(20)]. Figure 8 shows the visualization result in the axial T2 images.
The GPi and the adjacent optic tract and internal capsule can be visualized via inversion recovery and T2 images. Proper windowing of the images can also provide visualization of the internal capsule together with the GPi and GPe. For GPi DBS, implantation target choice may be different from that used for pallidotomies, which are typically located at the posteroventral portion of the nucleus. Implantation at that position may not be optimal for DBS because the DBS stimulation field may require higher amplitudes and potential spread to the internal capsule. Thus for DBS, a more anterior and lateral target is preferable, which will allow the stimulation amplitude to be increased without significant involvement of the descending white matter fibers. The optic tract courses ventrally to the globus pallidus and can be used as landmark for the approach (Fig.9).

By direct locating (SWI/7T MRI/DTI)

Since the high iron concentration in the STN causes T2* shortening and resonance frequency increasing, susceptibility-weighted imaging (SWI) which exploits the magnetic susceptibility differences of tissues, provides additional possible contrast mechanism to visualize STN...
without using anatomic landmarks. Using postprocessing techniques, a single SWI acquisition can generate 3 sets of inherently co-registered images: T2*-weighted maps of signal-intensity magnitude images phase image and a combination of the two. Vertinsky [21] and colleagues assessed the visibility as well as delimitation of STN using SWI and concluded that STN were directly visualized on SWI phase image.

Moreover, ultra-high MR system (e.g. 7T MR system) provides an increasing SNR, allowing much higher spatial and enhanced susceptibility contrast. Those small structures which cannot be well delineated at lower field have opportunity to be seen and segmented much more exactly. However, the clinical application of 7T MR still delayed by many critical problems such as the regional signal variation resulting from the inhomogeneous B0 and B1 field.

**By microelectrode recordings**

A fundamental purpose of microelectrode recording (MER) is to verify the stereotactic location of the target brain region for the electrode implantation. A neurophysiologist records neural activity as a microelectrode is advanced through stereotactic brain space and identifies specific nuclei on the properties of the neural signals recorded [22]. While not performed at all DBS centers, this verification process can help alleviate two limitations. First, the surgical target
cannot always be directly identified on preoperative imaging data. Second, the intracranial pressure changes once the burr hole is drilled, resulting in a possible shift of the subcortical structures, thereby altering the position of the target point in stereotactic space [23].

MER begins at various distances from the target. Take the target STN as an example, the distances between recording and STN range from several millimeters (Fig. 12B) to up to 40 mm (Fig. 1A), depending on whether striatal and/or thalamic activity is recorded. Findings depend on the obliquity of the planned tracks. When the entry point is more lateral, the track misses the striatum or thalamus, residing completely within the corona radiate and internal capsule (Fig 1B). When recording begins more proximally (~40 mm from above target) and with more medial entry points, the caudate is encountered with its characteristic pattern of phasically active units. Below this, the internal capsule is entered, from which occasional fibers may be recorded. More anterior tracks will pass in front of the thalamus, next encountering the Zona
incerta (ZI), in which small infrequent neurons may be recorded with low tonic firing rates. More posterior tracks pass into the thalamus, approximately 7mm above the STN. The shell of the thalamus contains the reticular nucleus with its characteristic bursting pattern discharges (15±19Hz). The ventral basal complex is encountered next, the cell of which fire at an average 28 Hz. These cells are easily distinguished from the STN itself as their firing rate is significantly lower, and the overall background of the thalamus is substantially quieter. After 1 to 2 mm, the STN is entered, characterized by an abrupt increase in background activity. Mean firing rates have been reported in the 34-74 Hz, with standard deviation is 25Hz [24]. Below the STN, the electrode traverse into SNr whose mean firing rate in most report is higher [25] than STN but in some notes is lower [26]. Rather, the pattern of neuronal activity, motor responsiveness, and background activity offer greater reliability in determining electrode location. These findings are mirrored in semimicroelectrode recordings [Fig 13], where the overall background of the STN provides a sharp contrast to that of the internal capsule and ZI above and the SNr below.

By macro stimulation tests

Following mapping via microelectrode recording we described above, macrostimulation is performed with either the microelectrode using current in the milliamp range, the uninsulated
tip of the inner guide cannula through which the microelectrode was passed, a dedicated macroelectrode (e.g. a radio-frequency ablation electrode), or DBS electrode.

Within the internal capsule, orofacial and/or appendicular contractions are noted, as are contraversive eye movements. Within the thalamus, various effects have been reported (e.g. vegetative effects) in some instances and a mild reduction in distal muscle tone ventrally [13]. Stimulation within zona incerta (ZI) and the fields of Forel can produce a decrease in rigidity at relatively low voltage thresholds (27). Stimulation in the STN produces the maximal clinical effects intraoperatively, however, and they are obtained at the lowest thresholds. Stimulation within SNr is generally without clinical effects, although some have observed decrease in rigidity and worsening of bradykinesia.

The distance and direction of refinement of initial targeting is related to the accuracy of the initial imaging and target calculation, as well as the technique and accuracy of the mapping procedure. One measure of both the inadequacy of the initial imaging, target calculation, and stereotactic technique, and the subsequent ability of physiological mapping to ‘correct’ these errors, is the amount of correction of the electrode position following mapping. Both microelectrode recording techniques and macrostimulation techniques can be used to correct the electrode position. Some groups relied solely on macroelectrode or microelectrode mapping to position the electrode optimally while some relied on combination of these two techniques. Does the use of mapping improve outcome? There are insufficient data available to determine whether any mapping at all, as opposed to pure anatomical targeting without modification based on intraoperative evaluation, is necessary for good results from STN DBS.
References


