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Review Article

# Engineering the Next Generation of Clinical Deep Brain Stimulation Technology

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ABSTRACT

Deep brain stimulation (DBS) has evolved into a powerful clinical therapy for a range of neurological disorders, but even with impressive clinical growth, DBS technology has been relatively stagnant over its history. However, enhanced collaborations between neural engineers, neuroscientists, physicists, neurologists, and neurosurgeons are beginning to address some of the limitations of current DBS technology. These interactions have helped to develop novel ideas for the next generation of clinical DBS systems. This review attempts collate some of that progress with two goals in mind. First, provide a general description of current clinical DBS practices, geared toward educating biomedical engineers and computer scientists on a field that needs their expertise and attention. Second, describe some of the technological developments that are currently underway in surgical targeting, stimulation parameter selection, stimulation protocols, and stimulation hardware that are being directly evaluated for near term clinical application.



## Introduction

Deep brain stimulation (DBS) is an effective clinical technology, positively impacting the lives of tens of thousands of patients worldwide, directly quantified by Medtronic announcing that their 100,000th DBS patient was implanted in 2012. DBS has FDA approval for the treatment of essential tremor (ET) [4], Parkinson's disease (PD) [42], dystonia [51], and obsessive-compulsive disorder (OCD) [22]. In addition, numerous clinical trials are currently underway or recently completed to evaluate its efficacy for other disorders, most notably epilepsy [18,41] and treatment refractory depression (TRD) [25,35].

The clinical outcomes achieved with DBS are a testament to the efficacy of the current device technology, surgical implantation techniques, and clinical programming strategies. For example, DBS for movement disorders can commonly provide greater than 50% improvement in clinical ratings of motor symptoms in appropriately selected patients [39]. However, DBS typically requires highly trained and experienced clinical oversight to achieve maximal therapeutic benefit in each patient [40]. In turn, an important and necessary step forward for wider scale use of DBS therapies is the development of assistive technologies that optimize its clinical implementation.

The inception of modern DBS is credited to [4], but the basic concepts date back to the 1960s (e.g. Refs. [16,23]). The most common clinical DBS hardware in use today is the Medtronic Activa system. However, competitive systems are currently available in Europe from St. Jude Medical (Libra system) and Boston Scientific (Vercise system). All of these clinical DBS systems consist of an implanted pulse generator (IPG) connected to a lead with multiple (4–8) cylindrical band electrode contacts at the distal end of the lead. A commonly used lead in clinical practice is the Medtronic 3389 model which has four platinum–iridium contacts separated by 0.5 mm spacing. Each electrode contact is 1.5 mm in length and 1.27 mm in diameter resulting in a surface area of ~6 $mm^2$.

## DBS surgery

Each DBS implant center follows their own specific surgical protocol, but the fundamental steps of the surgery consist of pre-

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operative target planning, electrode placement, and IPG placement [2]. Currently, the most common DBS procedure is to implant electrodes into the subthalamic region of the diencephalon for the treatment of PD (Fig. 1). The exact physiological mechanisms of this therapy, as well as the directly stimulated neural pathways explicitly responsible for therapeutic benefit, remain unknown [37].

The brain target location for electrode implantation in each hemisphere of each patient is initially determined using anatomical MRI data. These targeting scans are typically acquired in an outpatient visit prior to the DBS surgery. However, to identify a target point in the brain, the neurosurgeon must define a coordinate system that is compatible with their surgical instruments. To do this they rely on a stereotactic frame. The most common frame systems are made by Elekta (Leksell) or Integra (Radionics CRW). The frame is placed on the patients head, the morning before the surgery, and they are taken to get a CT and/or MRI with the frame in place. Fiducial markers associated with the frame allow for definition of common coordinate system used for all subsequent surgical steps (Fig. 1A). The head image acquired with the frame is then co-registered with the pre-operative anatomical MRI using a commercial neurosurgical navigation software package. The most common targeting software systems are made by Medtronic (StealthStation) or BrainLab (iPlan). These software systems enable interactive definition of the target point within the context of the MRI, as well as the surgical trajectory used to reach that point (Fig. 1B). Selection of these parameters enables the surgeon to adjust the mechanical features of the frame system such that the target can be reached during the operation.

The DBS electrode implantation surgery is typically performed with the patient awake. A burr hole is drilled in the skull, a guide canula is inserted into the brain, and a microdrive is used to advance the electrode to the target. The majority of DBS centers also perform microelectrode recording (MER) based physiological confirmation of the target prior to permanent placement of the DBS electrode (Fig. 1C). In addition, test stimulation through the implanted DBS electrode is typically performed to evaluate therapeutic benefit and possible side effects prior to fixing the lead in place. Final lead placement is commonly verified intra-operatively using fluoroscopy and/or post-operatively using CT. The IPG is then implanted in the subclavicular region and connected to the DBS electrode(s), typically in a follow-up procedure. Duration of the total DBS implant process is estimated at 4.5 h for a unilateral implant, and 6 h for a bilateral procedure [2].

A wide range of research efforts are currently underway to improve the surgical targeting of DBS electrodes. These efforts focus on alternative frame systems, improved imaging protocols, and advanced MER signal processing strategies. Traditional stereotactic frames represent the standard in DBS surgery; however, so called “frameless” systems have also been developed. Commercial versions of these systems are made available by Medtronic (Nexframe) and FHC (microTargeting). The primary benefit of using a frameless system is patient comfort. The mechanical accuracy of frame-based and frameless systems is the same (~1.5 mm error) [24], and clinical outcomes from frameless procedures are comparable to those achieved with traditional frame systems [8,28].

One of the more dramatic alternative surgical strategies currently under development is the concept of using intraoperative (a.k.a interventional) MRI to guide placement of the DBS electrode [30,46]. These procedures require a frameless MRI compatible aiming device and use direct visualization on the patient imaging data to verify lead placement. This facilitates the use of general anesthesia for the patient, which would be desired by most people, and can speed up the overall procedure. However, this requires a specially equipped OR with an interventional MRI, and small (or low contrast) anatomical targets can sometimes be difficult to visualize on the MRI. Commercialization of this concept is being spearheaded by MRI Interventions (ClearPoint).

High-field MRI (7T) is also beginning to make inroads into DBS surgical targeting [1,32]. The superior signal-to-noise ratio and image contrast that can be obtained at 7T can improve anatomic

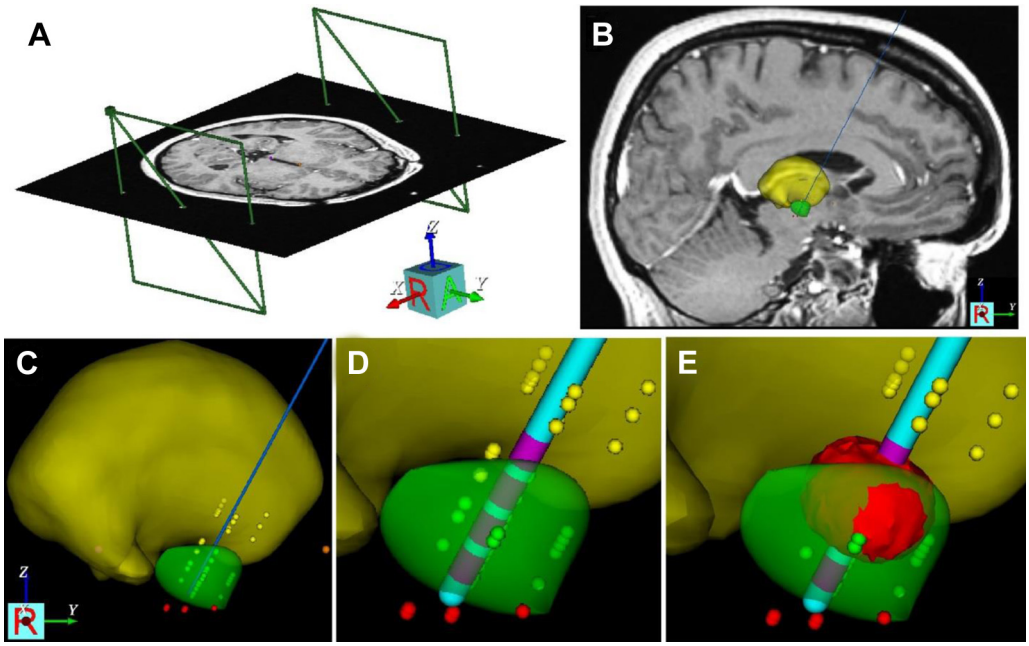


**Figure 1.** Deep brain stimulation. A) Stereotactic coordinate system is defined relative to the patient imaging data using the frame fiducal markers displayed in green. B) Atlas representations of anatomical nuclei are used to help identify the target (yellow volume – thalamus; green volume – subthalamic nucleus (STN)). The blue line represents the intended surgical trajectory. C) Stereotactic location of microelectrode recording data (thalamic cells – yellow dots; STN cells – green dots; substantia nigra cells – red dots). D) DBS electrode placement. Purple cylinders represent the electrode contacts. E) Red volume simulates the volume of tissue activated during therapeutic DBS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)