Chapter

Neuromodulation in the Age of Modern Neuroimaging Technologies

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Abstract

Most commonly used for the treatment of Parkinson's disease (PD), the deep brain stimulation (DBS) is a new neurosurgical method whose other applications are still under development. Neuroimaging has a variety of main roles in DBS including evaluating the final electrode contact position, localizing the target nucleus, and detecting complications. Despite being a neurosurgical method, successful DBS intervention is highly dependent on an appropriate neuroimaging technique. For achieving satisfying clinical results, DBS needs the presence of neuroradiologists. In this chapter, we have reviewed the role of neuroimaging in all stages of deep brain stimulation as well as the underlying mechanism in this domain.

Keywords: neuroimaging, neurostimulation, deep brain stimulation, functional neurosurgery

1. Introduction

Most commonly used for the treatment of Parkinson's disease (PD), the deep brain stimulation (DBS) is a new neurosurgical method which its other applications is still under development [1]. Neuroimaging has a variety of main roles in DBS including evaluating the final electrode contact position, localizing the target nucleus, and detecting complications.

Benabid et al. were the very first researchers who introduced the chronic high-frequency stimulation of the ventral intermediate nucleus (VIM) of the thalamus in early 1990s [2]. The authors used a subcutaneous pulse generator, which was implanted in the thoracic region, connected to chronic stimulating electrodes in the VIM for treatment of 6 patients with essential tremor and 26 patients with Parkinson's disease (PD). The patients maintained improvement up to 29 months. As the first clinical effort to introduce the chronic high-frequency stimulation of nuclei (deep brain stimulation), this study showed that this newly come up method could be used instead of common destructive surgeries such as thalamotomy.

Another similar technique, bilateral DBS of the subthalamic nucleus (STN), was then introduced by the Benabid team for the treatment of severe motor fluctuations and akinetic rigid Parkinson's disease [3]. In 2002, the USA food and drug administration (FDA) approved the treatment of Parkinson's disease by stimulation of bilateral STN and the stimulation of internal globus pallidus (GPi) was approved in 2003. Although advanced Parkinson's disease is the main indication for DBS, a number of different additional uses have been mentioned for DBS, such as Tourette syndrome, cluster headache, and dystonia as well as psychiatric indications such as major depression (MDD) and obsessive-compulsion disorders (OCDs).

Despite being a neurosurgical method, successful DBS intervention is highly dependent on an appropriate neuroimaging technique. For achieving satisfying clinical results, DBS needs the presence of neuroradiologists. In this chapter, we have reviewed the role of neuroimaging in all stages of deep brain stimulation.

2. Targets for DBS

A variety of indications and targets have been proposed for DBS since its starting era. Essential tremor and Parkinson's disease are among the most common and ancient indications of DBS, which are managed by stimulation of VIM nucleus [4–6]. On the other hand, STN and GPi are the most effective targets for Parkinson's disease DBS. It has also been reported that VIM DBS may relieve orthostatic tremor [6]. Tourette syndrome is another indication for DBS that is done through bilateral thalamic stimulation [7, 8].

Subthalamic nucleus (STN) stimulation by bilateral implantation of electrodes comprises a majority of DBS interventions for management of advanced Parkinson's disease [9, 10]. Intractable epilepsy is another described indication for STN DBS [11]. Recently, different psychologic disorders, such as OCD, have been discussed as possible indications for STN DBS [12]. Internal globus pallidus (GPi) is another target for DBS, which is more commonly indicated for managing dystonia and advanced Parkinson's disease [13–16]. Also, winter's cramp and Tourette syndrome have been managed by DBS of GPi [17–19]. Previous studies have shown that GPi DBS improves Yale Global Tic Severity Scale and reduces Tic in a range of 65–96%. An older reported indication for DBS is chronic pain for which a variety of targets have been proposed from internal capsule and periventricular gray matter to sensory thalamus [20, 21].

A variety of other targets have been come up for DBS in management of psychiatric disorders such as major depression or OCD [22–25]. On the other hand, cluster headache has been treated by hypothalamic DBS [26]. Also, seizures that are resistant to medical treatment have been managed by DBS of cerebellum, centromedian, or anterior nucleus of thalamus and hippocampus [26–28].

3. Pre-interventional imaging

Magnetic resonance imaging (MRI) is the most commonly used modality for pre-interventional brain assessment in Parkinson's disease patients who are candidates for DBS, whether STN DBS or bilateral GPi. Multiple lacunae, severe atrophy, or leukoencephalopathy are among the MRI abnormalities that contraindicate DBS surgery [29, 30]. Some features in MRI imaging are predictors of desired or non-appropriate postoperative results. For example, a normalized surface measure of mesencephalon is correlated with satisfying clinical effects of bilateral STN stimulation on motor disability in Parkinson's disease; while, a smaller surface of mesencephalon is more associated with non-desired results of stimulation [31]. Also, it has been mentioned that brain atrophy is not related to non-desired postoperative clinical results in patients who are candidates for bilateral STN stimulation. There is a supporting hypothesis for connecting these imaging features to post-interventional clinical results that believes that a small mesencephalic surface area is correlated with cognitive impairment and non-dopaminergic non-levodopa responsive axial motor symptoms that do not appropriately respond to STN stimulation.

Imaging modalities have an important role in targeting for DBS. Appropriate placement of electrodes is a sensitive and difficult neurosurgical technique, which involves highly skilled surgeons. In the first stage of DBS, anatomical landmarks are determined by MR imaging. Previously, invasive ventriculography was used to determine the anatomical landmarks for STN implantation; however, it is very uncommon these days [32]. MR imaging has two remarkable benefits: first of, it can be easily used for stereotactic targeting in DBS surgery and second, electrodes can be accurately implanted with no additional negative effects [33, 34]. Another option for targeting is MR imaging/CT fusion technique in which the data acquired from the two modalities are fused and MR imaging with stereotactic condition is not used anymore [35].

4. Imaging during intervention

Plain control radiographs are more commonly used by most of the neurosurgery teams during placement of implants to ensure that the electrodes are accurately following the predetermined pathway [36]. In addition, intraoperative use of MR imaging or CT scan has been recently developed for this purpose [37, 38].

Although it has remained a controversy, electrophysiological study of brain has been used intraoperatively for checking electrode placement in DBS surgery. Some neurosurgeons consider electrophysiologic mapping of the anatomic target during STN electrode implantation while others prefer not to apply it, as it prolongs the surgery and may be associated with risks and complications [39–41].

5. Postoperative imaging

In most of the cases, postoperative imaging is performed to detect the possible complications. CT scan is the most common modality that is used for this purpose. It seems that MR imaging has a higher sensitivity in comparison with CT scan for some complications; for example, electrode-related infections are more detected by MR imaging. Also, MR imaging correctly indicates the position of contact of implanted electrodes. MR imaging study provides a bunch of valuable data including the exact position of electrodes in case of clinical failure and also relationships between electrode and the target. Neurosurgeons more commonly register an atlas on postoperative MR imaging for checking the exact position of contact. Electrode heating is the most common complication of MR imaging, which is induced by electromagnetic waves [42, 43].

Post-interventional imaging has provided a remarkable source of data for discovering new therapeutic methods for many neurologic and psychiatric diseases. When undesired symptoms and manifestations are presented after DBS, researchers can assess the effect by imaging and this will lead to identification of new targets for managing a variety of disorders. It was found that bilateral hypothalamic DBS, which was used for treating morbid obesity, has evoked detailed autobiographic memories [44]. Also, the correlation of severe obsession and hyperactivity of caudate nucleus was found during intraoperative electrophysiologic study of caudate nucleus DBS in patients with OCD [45].

6. PET, fMRI, and DBS

Functional MRI (fMRI) is a neuroimaging modality with a wide range of application in both biomedical research and clinical studies. In addition to its high resolution for soft tissue imaging, MRI has the ability to assess physiological parameters including metabolites, diffusion, or hemodynamics [46]. Neuronal activity causes a secondary hemodynamic response, including a local vascular response, which can be measured by fMRI [47, 48]. fMRI has promoted our understanding about behavioral and translational neuroscience as it has provided human brain function maps in addition to conventional anatomical imaging.

When it comes to DBS, positron emission tomography (PET) scan is more preferred than fMRI as it provides a safer modality for studying patients during DBS intervention. PET is used for studying both mechanism and unexpected effects of DBS [49]. According to these facilities, PET has become a gold standard for imaging of in vivo neurochemistry.

Combination of fMRI and PET modalities has provided a terrific opportunity in research to understand the neurochemistry of brain and underlying biochemical nature of brain function.

7. Diffusion tensor imaging (DTI)

Diffusion tensor imaging is an emerging modality that enables us to characterize microstructure of white matter and this may help with further development of targeting methods and brain stimulation therapies [50]. The technology used behind the DTI is measuring three-dimensional movement of water molecules in biological tissue. DTI calculates diffusion of water in three dimensions by fitting a tensor to each voxel of a brain diffusion-weighted MR scan [51]. Three-dimensional visualization of brain white matter pathways can be provided by DTI-based tractography [52, 53]. This has resulted in better understanding of brain anatomical structure, which can be implied in neurosurgical procedures [54, 55].

Defining accurate position of targets is a key point in neurosurgical stimulation process. The role of DTI in detailed visualization of white matter becomes more important when the conventional imaging modalities cannot reliably show the putative target location [50]. Tractography-guided neuromodulation has been tried for DBS in patients with Parkinson's disease and dystonia. This will help surgeons with finding individual anatomic variations and so achieving better results.

8. Less invasive stimulation modalities

Neuromodulation carries a vast range of procedures from pharmacological interferences to the direct stimulation of brain with placed electrodes. Noninvasive brain stimulation (NIBS) devices work based on transferring electrical currents into the brain (usually cortex) through externally placed electrodes. These currents may be alternating or even created by magnetic fields [56]. In addition to its developed application in research, NIBS has dramatically entered to the clinical management of several neurologic/psychiatric disorders. Repeated trains of transcranial magnetic stimulation (rTMS) were first approved by FDA for management of major depressive disorders and obsessive-compulsive disorders, while migraine headaches are managed by single pulse TMS [56, 57].

A dynamic magnetic field is produced by TMS devices, which induces a consequent electric field through the skull and scalp. When this electric field is delivered to the motor cortex, neurons forming the corticospinal tract are depolarized at the junction of gray and white matter. In addition, axons in superficial layers of cortex including interneurons and thalamocortical afferents can be triggered by TMS pulses. TMS has effects on various brain neurotransmitter systems including their second messengers and receptors. Also, it promotes synaptic plasticity, which is a justification for TMS use in pain management. On the other hand, some previously published researches have indicated that TMS is effective in reducing frequency of epileptic attacks in patients with medically refractory epilepsy, without imposing any additional side effects. Another pilot study holds the belief that TMS in combination with EEG is an appropriate method for developing quantitative biomarkers of cortical hyperexcitability in patients with epilepsy [58].

A considerable problem with application of rTMS is its variable effects among different patients [59, 60]. This makes the research results' replication a problem and application of rTMS to clinical therapeutic setting a controversial issue. When we use rTMS in a precise cortical area, it will equally affect all the neuronal populations and consequent behaviors involving that area [61]. Therefore, combination of EEG and rTMS seems to be an appropriate method in order to specify the rTMS effects in patients through direct measurement of cortical responses to TMS pulses [62]. This helps with measurement of TMS-evoked potentials (TEPs) and the meantime effects of TMS on the recording EEG. Various TEPs' components are a reflection of activity in a precise area of cortical neurons. So, this may result in development of more selectively targeted forms of rTMS in non-motor areas of the cortex.

Transcranial direct current stimulation (tDCS) is another form of noninvasive brain stimulation techniques that is easily available and not extensive, while the exact mechanism of action has not been yet discovered [63, 64]. In this method, electrodes are placed on the scalp and they conduct weak prolonged (about 10–20 min) currents to brain tissues. Indeed, neuronal excitability is modulated in a polarity-specific manner by tDCS [65]. The modulatory effects of tDCS are the main role considered for this procedure as it shifts membrane polarity resulting to modifying the neuronal discharge. There are two subdivisions: anodal tDCS increases the rate of spontaneous neuronal firing by depolarizing resting membrane potential, while cathodal tDCS shifts the resting membrane potential to hyperpolarization, which leads into decreased cortical excitability [66]. tDCS has approved improving effects on patients with various types of anxiety disorders such as social anxiety disorders, generalized anxiety disorders, and anorexia nervosa as well as major depression and chronic pain [67–69].

Besides the proved applications of tDCS in previous studies, the effect of sham tDCS has not been yet completely assessed. Some previously conducted sham-controlled studies have reported inconsistent results with placebo response, which make this idea more important [70].

9. Neuroimaging and neurosurgical treatment of psychiatric disorders

Progresses in neuroimaging have resulted in developing a notable amount of new indications of DBS for psychiatric disorders. Discovering new functions and relationships for internal capsule, cingulate cortex and their networks is a result of modern neuroimaging techniques. In the major part of the situations, nodes of these networks are in the regions that are responsible for functional changes in psychiatric pathology that kind of confirms the benefits of conventional capsulotomy and cingulotomy [71].

These days, personalized medicine has become the most commonly mentioned subject in the modern medicine. All the medicine-related fields are trying to find ways that help with individualized treatment of the diseases, thus treating patients instead of diseases [72]. So, psychiatrists are following this trend and modern neuroimaging techniques may help them with finding proper treatment for each patient [73]. So far, neuroimaging was used only for checking the proper placement of electrodes and retrograde evaluation of interventional mechanisms; however, these modalities will be used for planning new treatment methods and targets for DBS in near future. Neuroimaging can provide lots of valuable data about connectivity and regional volume in each patient. Thus, it not only helps with choosing the most appropriate approach in psychiatric neurosurgery but also simplifies prediction of interventional outcomes [74–76].

Looking at the recent published studies around neuroimaging, we found out that developing neuroimaging techniques is leading to the age of "precision surgery." In this period of time, neuroimaging will change the face and approach to electrode implantation and patient selection as well as selection of surgical targets throughout individualized neuroanatomy extracted from modern neuroimaging modalities and technologies [74, 77, 78].

10. Conclusion

As the researches are getting more informative, more patients are going under DBS intervention especially for treating Parkinson's disease. In addition, as the modern technologies are developed, more new applications and targets are getting introduced for DBS. So, neuroimaging has a notable role in preoperative and postoperative sections as well as during DBS intervention. Further researches are required to discover more efficient imaging modalities that will lead to discovery of new targets and indications for DBS and functional neurosurgery.

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