Integrating Diffusion Tensor Imaging-Based Tractography into Deep Brain Stimulation Surgery: A Review of the Literature

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Key Words

Deep brain stimulation · Psychosurgery · Diffusion tensor imaging · Tractography · Movement disorders · Connectivity

Abstract

Background: It has been generally accepted that deep brain stimulation (DBS) not only acts in the nucleus where it is being applied, as initially thought, but that chronic stimulation activates axons located in its scope, and that this activation can exert its effects in distant areas. Considering this, DBS target identification should be made based on techniques that identify white matter tracts, such as tractography, rather than only by identifying specific nuclei on conventional magnetic resonance imaging. **Methods:** In this study, we performed a review of the literature on the use of tractography in DBS surgery and provide an overview of the main results. **Results:** Tractography has been used in the field of DBS to help clarify relevant aspects in the selection of targets and in evaluating its therapeutic effects in movement disorders, psychiatric diseases and pain. **Conclusions:** Studies are scarce so far, but they have provided data that, if confirmed, may optimize DBS surgery. Tractography might become a routine tool for DBS surgery in the near future.

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Introduction

Chronic deep brain stimulation (DBS) has become a widely used surgical treatment for an increasing number of medication-resistant neurological and psychiatric disorders [1]. There are studies that have shown that DBS not only inhibits the neuronal activity in the nucleus where it is being applied, as initially thought, but that chronic stimulation produces an activation of axons located in its scope, and that this activation can exert its effects in distant areas [2]. Although the net effect of the DBS would be a sum of its effects on local and remote structures, which is difficult to determine [2], it has been suggested that such fiber tract activation might override the transmission of pathological bursting and oscillatory activity through the stimulated nuclei [1].

Considering this, DBS target identification should be made using techniques that identify white matter tracts, rather than only by identifying specific nuclei on conventional magnetic resonance imaging (MRI) [3], hence the transcendence that integrating diffusion tensor imaging (DTI)-based tractography might entail.

Tractography provides 3D graphic reconstructions of the cerebral white matter fibers via DTI. DTI is a tech-

Table 1. Published studies on tractography and DBS surgery

First author	Year	Title	Patients
Hunsche [51]	2013	Tractography-guided stimulation of somatosensory fibers for thalamic pain relief	4
Klein [24]	2012	The tremor network targeted by successful VIM deep brain stimulation in humans	12
Schweder [21]	2010	Chronic pedunculopontine nucleus stimulation restores functional connectivity	1
Coenen [28]	2011	Individual fiber anatomy of the subthalamic region revealed with diffusion tensor imaging: a concept to identify the deep brain stimulation target for tremor suppression	1
Coenen [18]	2011	A role of diffusion tensor imaging fiber tracking in deep brain stimulation surgery: DBS of the dentato-rubro-thalamic tract (DRT) for the treatment of therapy-refractory tremor	1
Lujan [30]	2012	Axonal pathways linked to therapeutic and nontherapeutic outcomes during psychiatric deep brain stimulation	7
Pouratian [25]	2011	Multi-institutional evaluation of deep brain stimulation targeting using probabilistic connectivity-based thalamic segmentation	6
Sudhyadhom [7]	2012	Delineation of motor and somatosensory thalamic subregions utilizing probabilistic diffusion tractography and electrophysiology	–
Barkhoudarian [17]	2010	A role of diffusion tensor imaging in movement disorder surgery	3
McNab [31]	2009	Reduced limbic connections may contraindicate subgenual cingulate deep brain stimulation for intractable depression	1
Sedrak [6]	2008	The role of modern imaging modalities on deep brain stimulation targeting for mental illness	15
Johansen-Berg [42]	2008	Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression	9
Owen [50]	2008	Preoperative DTI and probabilistic tractography in four patients with deep brain stimulation for chronic pain	4
Owen [3]	2007	Preoperative DTI and probabilistic tractography in an amputee with deep brain stimulation for lower limb stump pain	1
Butson [69]	2006	Predicting the effects of deep brain stimulation with diffusion tensor based electric field models	1

nique that is based on MRI, capable of determining the trend of the diffusion of water particles in the different directions and, therefore, the main direction of a bundle of white matter fibers contained in a voxel. It is a non-invasive technique that is gaining popularity because it allows the delineation of white matter tracts in vivo and evaluation of the connectivity of different brain areas [4]. There are methods that, incorporated within the tractography technique, can predict the volume of tissue activated by DBS on brain tracts. This could help develop accurate predictions of the effects of DBS in brain regions distant from the target and foresee the possible adverse effects produced by the stimulation as it increases [5].

The number of published studies in which tractography has been used for selecting DBS targets, or for the study of the pathways involved in their therapeutic action, is scarce (table 1). The aim of this paper is to review the literature on the use of tractography in DBS surgery and to provide an overview of the main results.

Tractography Limitations

Tractography is a relatively new technique, and experience with it around the world is relatively scarce. It is currently questioned for its possibly low correlation with anatomical structures and poor reproducibility [2]. Sedrak et al. [6], in 2008, used tractography to determine the connectivity of several DBS targets for neurological and psychiatric disorders with other brain areas and to analyze the correspondence of these results with known data through other techniques. The studied areas were the cingulate gyrus, Brodmann area 25, amygdala, posterior hypothalamus, orbitofrontal cortex, nucleus accumbens, anterior limb of the internal capsule and dorsomedial thalamus in 15 patients undergoing stereotactic surgery for movement disorders. The authors obtained connectivity patterns consistent with those of other tractography studies and with previously known data, and therefore concluded that tractography is reliable for identifying connectivity patterns in the brain and for planning DBS

targets. In another study comparing tractography with neurophysiological monitoring using microelectrodes, an overlap in certain areas such as the thalamus was obtained, whereas it showed poorer correspondence with the neurophysiological results in other areas [7].

It seems increasingly likely that tractography might yield reliable and reproducible results if it is performed under certain conditions [8, 9]. In a study in which the probabilistic method was used to analyze the reproducibility of tractography from a qualitative perspective, the results were satisfactory in 6 out of 8 subjects if tractography was used for segmenting the thalamus. However, for the other 2 cases, the authors obtained a poor segmentation, which was probably related to the lower quality of the obtained data [8]. In another study by Traynor et al. [9] in 2010, the authors analyzed the reproducibility of thalamic segmentation from a quantitative point of view in a single subject. Multiple analyses were performed using the same database obtained from the subject, varying the probabilistic tractography algorithm conditions. Subsequently, the authors conducted an analysis of other data sets that were acquired independently from the same subject. Thalamic segmentation also proved to be very reproducible using 6 target cortical regions, although the reproducibility was reduced when the number of target regions increased, especially in the medial and posterior thalamus. When the analysis was extended to a group of normal subjects, the results showed a high degree of overlap, particularly in thalamic regions with connections to the frontal, parietal, temporal and precentral cortex.

Tractography in DBS Surgery

Movement Disorders

Since the 1980s, when the first patient was treated with DBS for essential tremor, DBS has been established as a standard therapy for movement disorders that cannot be controlled with medication [10–13]. Currently, there are over 100,000 patients worldwide treated with DBS for movement disorders [11–14]. Although DBS controls the main symptoms, some manifestations of these disorders do not improve with stimulation in the usual targets [15]. Furthermore, there is still no certainty about the pathways involved in the mechanism of action of DBS, and which are responsible for many of its side effects [16]. Tractography has begun to be used to investigate these issues, with some results [17].

In a paper published by Barkhoudarian et al. [17] in 2010, the authors studied 3 patients undergoing stereo-

tactic surgery for movement disorders by tractography [one patient had Parkinson's disease (PD), another had essential tremor and the third one had dystonia related to cerebral palsy] to establish the pathways involved in the therapeutic effect and side effects of the stimulation. The stereotactic targets were the subthalamic nucleus (STN), ventral intermediate nucleus (Vim) and globus pallidus, respectively. The authors selected the contacts with an obvious clinical effect in every patient. In patient 1, the fibers that left the active contact (in the STN) ended in the precentral and premotor cortex, in particular in the area responsible for hand movements. However, increasing the size of the volume of interest (VOI), which simulates an increase in the stimulation voltage, incorporated additional fiber tracts connected laterally to the prefrontal and parietal cortex as well as to the occipitofrontalis bundle. In addition, there appeared to be some tracts approaching the region of the frontal visual fields (Brodmann area 8). In patient 2, undergoing DBS of the Vim, tracts were observed in the premotor and motor cortex when the small VOI was used. By increasing the VOI, additional extensions to the prefrontal, supplementary and motor cortex as well as the parietal lobes and cerebellum were obtained. In patient 3, with DBS in the globus pallidus, there were connections to the motor, prefrontal and parietal sensory cortex and to the eye fields and cerebellum when the VOI was increased. The authors observed an association between certain motor side effects and activation by the stimulation of fibers directed to the premotor and supplementary cortex in this patient. However, it was not possible to establish specific relationships between the cortical regions affected by increasing the size of VOIs and the occurrence of side effects in other patients [18].

Parkinson's Disease

It is generally accepted that one of the optimal locations for DBS electrode implantation for PD is the posterolateral area of the STN. However, axial symptoms and gait disturbances are generally not adequately controlled with stimulation in the STN [15]. Recently, the region of the pedunculopontine nucleus (PPN) has gained importance as a potential target for patients with PD and gait disorders and falls as the predominant symptoms [19]. In principle, it is thought that the presence of PPN connections to the globus pallidus can help counteract the inhibitory influence on it observed in PD [20].

The PPN has been studied using tractography to identify its main connections [20, 21]. In a study by Aravamudan et al. [20], the authors studied the brain regions with

greater connectivity to the PPN in 8 patients, placing a VOI in the PPN in each hemisphere and considering only those that were present in 4 of the 8 subjects. PPN connections existed to the cortex, basal ganglia, cerebellum and spinal cord, with a similar distribution to those demonstrated in primates. In a longitudinal study published by Schweder et al. [21] in 2010, the authors examined the long-term effect of low-frequency bilateral stimulation in the connectivity of the PPN region in a patient with PD and frozen gait. Probabilistic tractography and a topographic map were used to locate the region of the PPN through the identification of the medial lemniscus and the superior cerebellar decussation. The preoperative connectivity in the patient was altered compared to healthy controls, showing a lack of connectivity with the cerebellum and an increased connectivity with the pons above the level of the middle section of the fourth ventricle. The connectivity was excessive relative to that of the healthy controls in the motor cortex, particularly in the area of the cortical homunculus representing the lower extremities. Upon stimulation, the connectivity to the cerebellum increased and that to the brainstem significantly decreased; thus, it normalized compared to healthy subjects [22].

Tremor

Tractography has contributed to the implementation of DBS surgery for tremor in two fundamental ways. First, it has served to more precisely characterize the circuits involved in the genesis and treatment of tremor and to identify the most effective thalamic regions for DBS application based on their connectivity. Secondly, the dentatorubrothalamic tract (DRT) has been identified as a possible target for the application of DBS, as an alternative to the Vim or ventral oral thalamic nucleus [18].

The Vim of the thalamus is the typical target structure, among other nuclei in the ventral thalamus, typically used for the treatment with DBS for refractory tremor [23]. Several studies have been conducted to characterize the neural network involved in the pathogenesis and treatment of tremor, based on the analysis of the connectivity from these thalamic areas [8, 24, 25]. In a study conducted by Klein et al. [24], the authors studied 12 patients undergoing DBS of the Vim for disabling tremor by tractography. The tractography was initiated at the effective contacts and produced a highly reproducible network of connectivity to motor regions comprising cortical and subcortical structures, the cerebellum and the brainstem. In this group, the most effective contacts were found in the thalamic area that was more connected to the prima-

ry motor cortex. However, in a paper published by Pouratian et al. [25] in 2011, although the authors started from the same hypothesis, the results suggested that the primary target for tremor should be the thalamic region, with the highest probability of connectivity to the premotor and supplementary cortex. For that, the authors studied 6 patients who had been operated on for the treatment of tremor in the upper extremities. All electrodes were implanted by traditional methods (based on the selected coordinates and intraoperative findings of stimulation) and programmed for optimum efficiency. The results showed that the most effective contacts were those situated in tracts ending in the supplementary and premotor cortex [8, 25].

Some studies indicate that the posterior area of the STN as well as the caudal region of the zona incerta can be equally or even more effective targets for the treatment of certain forms of tremor, associated with a lower probability of dysarthria and other incapacitating side effects compared to DBS of the Vim [16, 23, 26]. In fact, some authors concluded that the efficacy of the lesion and Vim DBS could be mediated by stimulation of the DRT, consisting of the projections from the cerebellum to the contralateral thalamus [27].

There are several studies where tractography was used to confirm this hypothesis and to identify the DRT as a target for the implantation of DBS for the treatment of tremor. Coenen et al. [18], in 2011, implemented this methodology in 2 cases: a patient with PD and another patient with dystonic cephalic tremor. The authors used probabilistic tractography and identified the area of the pyramidal pathway. Then they tried to find the DRT by applying a VOI in the brainstem, including the midline and the cerebral peduncles. The resulting fibers were selected following the superior cerebellar peduncle, and another VOI was applied incorporating the ipsilateral dentate nucleus. As a final step, a third VOI was placed around the fibers that reached the precentral gyrus. The DRT was identified in the vicinity of the pyramidal tract and medial lemniscus. Merging data from postoperative CT revealed the exact location of the DBS electrode with respect to the adjacent fiber tracts. The evaluation of the electric fields surrounding the electrodes allowed the identification of the DRT as the target of stimulation [18, 28].

Psychiatric Disorders

DBS is being used for the treatment of an increasing number of psychiatric disorders [29–33]. It has confirmed its effectiveness in a significant percentage of patients with obsessive-compulsive disorder (OCD), major

depression and Tourette's syndrome, and it is being investigated as a treatment for obesity and addiction [34–41].

In recent years, different targets have been proposed for the surgical treatment of depression and OCD. These targets have emerged mostly because they showed abnormalities on positron emission tomography (PET) in chronic patients that disappeared when the patients responded to different treatments [29, 32, 42, 43]. The main targets used for depression and OCD are the subgenual cingulate, the anterior limb of the internal capsule and the nucleus accumbens, which have a very similar efficiency (50–60%) and need the application of high voltages of stimulation to produce clinical benefits [28]. The multiplicity of targets and their comparable efficacy raises questions about what the anatomical structures explicitly responsible for the therapeutic benefits of DBS are [44].

According to Coenen's group, the fundamental structure responsible for the therapeutic action of these targets could be the medial forebrain bundle (MFB), which is part of the motivation and reward system. This group performed a theoretical study in 2012, in which they theoretically represented (using a probabilistic tractography map) the white matter tracts affected by the stimulation of the three abovementioned targets and their relationship to the MFB [18, 28]. They showed that the MFB is partially included in the electric field at different target sites of depression by 92% [18, 28].

DTI has also been used to identify axonal pathways activated by stimulation and its correlation with the individual clinical outcome [42, 43]. In a study conducted by Lujan et al. [30] in 2012, 7 patients with depression treated with DBS of the ventral anterior internal capsule and ventral striatum were studied. The treatment responders showed 5 pathways medial and lateral to the ventral striatum, or dorsal and lateral to the nucleus accumbens, which were similarly activated by DBS. There was also a common pathway activated in those who had not responded to treatment. In another study by Johansen-Berg et al. [42] in 2008 to identify anatomical pathways underlying the therapeutic response, the authors studied the connections between the region of the anterior cingulate cortex (ACC) and the areas that change their metabolism in response to stimulation for depression. They also analyzed the connectivity of the areas surrounding the active contacts in 9 responders in order to define the anatomic pathways likely affected by the stimulation. The authors found that although most of the connections were common to the whole ACC area, the probability of a connection differed depending on the location within that area.

Connections to the amygdala, hypothalamus, nucleus accumbens and orbitofrontal cortex were more likely in the posterior subgenual region. Connections to the medial and frontopolar ACC were more prominent in the pregenual cingulum. They also found that all active electrodes were located in the subgenual area [42].

As previously mentioned, some studies suggest the existence of a reduced fractional anisotropy in patients with bipolar disorder and depression [45–48]. McNab et al. [31] proposed that different pathological connectivity patterns could present a different response to treatment with DBS. In 2009, they reported a case of a patient with bipolar disorder who had suffered a stroke in the dorso-medial thalamic nucleus and since then had resistant depression. He underwent DBS of the subgenual region, which was not effective for the relief of his symptoms. The authors used probabilistic tractography to analyze the anatomical connections between the subgenual region and the rest of the brain, as well as connections between the amygdala and the stroke area, and its contralateral counterpart. They placed VOIs in these areas, and in each of the subgenual contacts in the area, and found that there were no pathways between the amygdala and the stroke, whereas some were found between the contralateral homologous regions. Connections were observed between the subgenual region and the amygdala, extending beyond the temporal lobe. However, the pathways of the amygdala to the subgenual region seemed reduced in the right hemisphere compared to the left. The patient died at 16 months after surgery, and a postmortem study with 3-tesla MRI was performed at a much higher resolution, with similar results. The authors concluded that the apparent reduction of structural connectivity of the ACC posterior subgenual region to the amygdala in the right side could have prevented the effectiveness of the treatment of the depressive symptoms by DBS [31].

Pain

The periventricular/periaqueductal gray (PVG/PAG) area has a key role in the modulation of nociceptive stimuli, since it is a basic structure of the central pain-inhibitory system [49]. It was one of the first areas in which DBS was successfully applied as a treatment for chronic pain [49]. However, there are still some outstanding issues related to the optimal stimulation site for different types of pain. Also, some studies have suggested that the PVG/PAG area might have a somatotopic organization, which is amenable to being studied with tractography [3, 50].

Owen et al. [3, 50] conducted two consecutive studies in order to identify the pathways involved in the DBS of the PVG/PAG for chronic pain. In 2007 [3], the authors studied a single patient, and in 2008 [50], 4 other patients undergoing DBS in the PAG/PVG area, with a good response. The chosen target was 2–3 mm lateral to the wall of the third ventricle, 2 mm above the level of the posterior commissure and at the level of the superior colliculus. Probabilistic tractography was performed, and areas of interest covering the 4 contacts were located on postoperative MRI. In the first case, they found connections from the active contact (contact 0) to many areas related to pain circuits, such as the orbitofrontal cortex, amygdala, anterior temporal gyrus, putamen, dorsomedial thalamus, reticular nucleus and anterior nucleus of the thalamus [3]. In particular, contacts 0 and 1 showed connections to the structures involved in processing the affective dimension of pain, such as the amygdala, orbitofrontal cortex and midanterior ventral posterolateral thalamic nucleus.

In the second study [50], connections were found in 3 of the 4 patients to the dorsomedial thalamus, precentral gyrus and central sulcus. Other areas observed in half of the patients were the superior frontal gyrus, superior temporal gyrus, anterior nucleus of the thalamus, putamen, internal capsule and superior colliculus as well as the centromedian thalamic and ventral posterolateral nucleus, caudate nucleus and cerebellum.

The authors concluded that the response of the patients was probably due to a modulation of the affective components of pain, rather than only of the sensory circuits. While some of the patients showed more connections to the sensory areas and the dorsomedial nucleus, other cases had balanced connections to both anterior and dorsomedial nuclei of the thalamus, which, according to the authors, could be related to different trajectories of the electrodes or to a somatotopy in the PVG/PAG [3, 50].

Another group of researchers [51] used deterministic tractography for the planning of DBS of the spinothalamic tract, which, due to its low contrast, cannot be visualized with conventional MRI. They performed DTI in 4 patients with thalamic pain, at the level of the posterolateral internal capsule. Tractography helped to choose a target region in such a way that the DBS electrode covered, at a length of over 20 mm, the sensory fiber from the target in the direction of the entry point. At the 12-month follow-up, a pain relief of more than 40% by rating on a visual pain scale was achieved in 3 of the 4 patients [51].

Tractography may allow a better characterization of different pain syndromes, of the degree of involvement of the emotional components of pain in each patient and of the somatotopy of the PVG/PAG, which might help to optimize the selection of targets for chronic pain.

Discussion

Tractography has been used in the field of DBS to help clarify relevant aspects in the selection of targets for stimulation. Studies are scarce so far, but they have provided data that, if confirmed, may be useful to optimize DBS surgery. White matter tracts such as the DRT and the MFB have been identified as potential targets for stimulation for tremor and depression, respectively [14, 20, 24, 28, 42, 43, 52, 53]. The selection of optimal subregions within the usual targets, based on their connections with other brain areas, has advanced as well for the treatment of abnormal movements and pain [3, 18, 20, 50]. If these results are confirmed, it is likely that tractography may be routinely used for the selection of targets in the near future.

The development of increasingly accurate research methods has advanced our knowledge about the brain structure and function. Thus, the current view of the brain is that of a group of cortical and subcortical interconnected structures forming a neural network which serves as the basis for the execution of brain functions. There is growing evidence that this network can be variable over time and modifiable by experiences of an individual [2].

Recent studies indicate that interruptions of integration or segregation within these network nodes may underlie the generation of certain neurological and psychiatric diseases, leading to changes in connectivity. In PD, for example, an increased connectivity between the cortex and the STN with respect to healthy subjects has been shown in functional MRI (fMRI) studies [54–56]. This increased connectivity seems to be related to the onset of phase coherence in the beta band (13–35 Hz) observed in these patients, which has been, in fact, correlated with the severity of tremor, bradykinesia and rigidity that they present [57]. Other studies have shown an increase in connectivity between the supplementary motor and primary motor areas and the cerebellum, as well as decreased connectivity between the putamen and cerebellum. In patients with dystonia, a decreased connectivity in the cerebellar projections to the ventral thalamus and from the globus pallidus to the cerebellum is characteristic [58]. In

cervical dystonia, an asymmetry in connectivity has been found when comparing both sides [59]. Changes of connectivity have been observed in certain psychiatric conditions; for example, there seems to be a decrease in connectivity between the amygdala and the prefrontal cortex in patients with borderline personality disorder [33]. Studies suggest that schizophrenic patients have a significantly lower overall connectivity than healthy controls, while patients with bipolar disorder have an intermediate global connectivity which is significantly different than in schizophrenia patients and healthy controls [46, 60]. In fact, the low global connectivity in all patients appears to be associated with worse clinical and neurophysiological functioning [6, 33, 60, 61].

If a pathological synchronization of certain circuits appears to be a possible etiological mechanism for neurological and psychiatric diseases, the desynchronization of these circuits with the restoration of normal functional connectivity could be a therapeutic strategy and has been established as one of the fundamental mechanisms of action of DBS [2, 57]. In fact, many of the subcortical structures that are stimulated by DBS as a treatment for neurological diseases show a generalized dense connectivity and may represent a constituent base node of the network [6, 33]. According to this, techniques that determine the connectivity status of key brain areas, and that are able to assess whether the normal circuit connectivity after a treatment has been restored, might become fundamental tools for DBS surgery [2, 22].

Studies comparing patients with neurological and psychiatric diseases and healthy volunteers using PET and fMRI have shown hyper- or hypoactivity in specific functional pathways and functional normalizations of these areas with pharmacological and nonpharmacological

treatment options [62–66]. Although this approach might oversimplify the neurobiological interplay between structural and functional conditions, these findings have served as a rationale for the successful application of DBS in these areas for certain disorders [29, 39]. The relationship between functional connectivity (studied by fMRI and PET) and structural connectivity (as shown by tract-tracing studies and DTI) has not yet been elucidated. Structural connections between brain regions are readily identified in nonhuman primates by using tract-tracing methods and DTI, as tracing studies in humans are not feasible because the most effective tracers require antemortem injections [67, 68]. It has been suggested that functional connectivity reflects structural connectivity to a large degree; however, it appears that functional connectivity between regions with known or presumed structural connections varies depending on several contextual variables [67, 68]. Whether DTI is able to reflect functional connectivity changes induced by DBS needs to be confirmed.

Conclusions

Tractography has emerged as a noninvasive technique capable of informing about the state of brain connectivity and the 3D location of white matter tracts in the brain. It has been used in the field of DBS to help clarify relevant aspects in the selection of targets and in evaluating the therapeutic effects of the stimulation. Studies are scarce so far, but they have provided data that, if confirmed, may be useful to optimize DBS surgery. It is possible that tractography may be routinely used in the selection of targets and the evaluation of results of DBS in the near future.

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