Improving surgical treatment for movement disorders
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Chapter 1

Introduction
1. Surgical treatment of movement disorders

Movement disorders are a group of neurological diseases and syndromes affecting the control of movement, resulting in either an excess of movement or a paucity of voluntary and automatic movements, unrelated to weakness or spasticity. Among the most common movement disorders are Parkinson’s disease (PD), with a prevalence of approximately 1 to 3% among persons 60 years of age and older, essential tremor (ET) with an estimated prevalence of 0.3 to 4% above the age of 40 and dystonia with an estimated prevalence of 152 per million.

The medical treatment of movement disorders is sometimes unsatisfactory. Especially in the advanced forms of the diseases, available medical treatments produce only partial or temporarily improvement, or carry unacceptable side effects. Up to 70% of PD patients who initially respond well to oral treatment with levodopa or dopamine agonists, develop medication-related motor complications within 10 years of disease. Dystonia appears as focal when it occurs in only one body region (e.g. cervical dystonia), segmental when it occurs in adjacent body regions, hemidystonia or generalized dystonia. The treatment of choice for focal forms of dystonia consists of intramuscular infiltration of botulinum neurotoxin (BoNT). This treatment needs to be repeated at regular intervals of about 3 months. BoNT fails to produce improvement or loses effectiveness in around 25% of patients. BoNT treatment is not an option for patients with generalized dystonia. For these patients, oral treatment with anticholinergic agents or benzodiazepine can be used but is rarely satisfactory, especially in the long term. Moreover anticholinergic treatment is rarely tolerated at higher dosages due to the high incidence of side effects, including confusion, drowsiness, dizziness, and blurred vision.

For patients with ET, treatment with propranolol or primidone is only effective in 50% to 70% of patients and achieves an average tremor reduction of 50% to 60%. For all these movement disorders, stereotactic surgical treatment, ablative or Deep Brain Stimulation (DBS), can be a good alternative.

Stereotactic surgery for movement disorders started with ablative procedures, lately largely replaced by DBS. DBS is nowadays an approved treatment for PD, dystonia, and ET, and is performed also for a growing number of other neurological and psychiatric indications, in many centres worldwide. The number of patients that have received DBS worldwide since 1997 is estimated to be larger than 80,000.

2. Deep brain stimulation

Stereotactic brain surgery makes use of a three-dimensional coordinate system to localize and target small areas inside the brain. Targeting is based on coordinates derived from stereotactic atlases and on direct visualization of structures on brain imaging. Preoperative frame-based MRI is used to identify the target structures, and compute 3D coordinates based on an external reference system (frame). Targeting can be functionally refined by
the use of intraoperative microelectrode recordings (MER) and test stimulation. For this purpose, surgery is performed with patients awake and off medication. Microelectrode recordings are performed by introducing up to 5 microelectrodes along parallel tracks, which are advanced in small steps (e.g. 0.5 mm) toward the imaging-defined target area. Microelectrode recordings provide neurophysiological information about the neuronal activity in the nearby area. While providing useful functional information for the refinement of the target, MER might theoretically increase the chance of bleeding due to the increased number of intra-cerebral tracks. In addition they require specific expertise and additional surgical material (microelectrodes, connection wires, recording machine). For these reasons they are not used in some centres.

During surgery, test stimulation is also performed at different locations, in order to identify the location with the best therapeutic window for deep brain stimulation, with the lowest threshold for beneficial effects and the highest threshold for side effects.

Stereotactic surgery can be used to perform different interventions such as ablative procedures or deep brain stimulation. Ablative stereotactic procedures consist of lesions of deep brain structures, while DBS implies the implantation of electrodes and the internalization of a system for chronic stimulation.

In comparison to ablative procedures, DBS offers the considerable advantage of a bilateral approach, which is not advised for ablative procedures due to the high rate of permanent complications. For this reason, and for the possibility to adapt the produced effect and side effects by tuning the stimulation parameters, DBS has nowadays almost replaced the ablative procedures. Moreover, in randomized studies DBS was shown to have better effect than lesions for the treatment of Parkinson’s disease and essential tremor.

2.1 DBS Technique
After intraoperative microelectrode recordings and test stimulation, the test electrodes are replaced by a permanent DBS electrode for chronic stimulation. The definitive electrode is anchored to the skull and subsequently, the internal pulse generator is implanted subcutaneously in the chest and connected to the intra-cerebral electrodes by means of extension wires, under general anaesthesia. After surgery, a CT scan can be performed to check for the occurrence of complications, such as haemorrhage or pneumocephalon, and to verify the electrode position. The latter is obtained by image fusion of postoperative CT images to the preoperative frame-MRI.

After surgery, the selection of the most appropriate parameter settings is performed on an outpatient basis.
3. DBS for Parkinson’s disease
Surgical stereotactic interventions for PD began with ablative surgery of the ventral intermediate nucleus of the thalamus (Vim) for the suppression of tremor in the 1940’s. Surgical treatments were almost abandoned after introduction of levodopa therapy. Later on, the recognition of levodopa-related complications for patients in the advanced stage induced a re-emergence of stereotactic surgery. Targets for ablative surgery in the 1990’s were the ventrolateral thalamus, the globus pallidus internus (GPI), and the subthalamic nucleus (STN).

The observation of temporary suppression of Parkinsonian tremor during intraoperative test stimulation, lead to the introduction of implantable systems for chronic stimulation.

3.1 STN DBS
Nowadays, the most commonly used target for DBS in PD is STN. The STN target was proposed based on anatomical considerations and animal studies. While stimulation of the Vim would only improve tremor, STN stimulation has proven effective for the three cardinal symptoms of PD: tremor, rigidity, and bradykinesia. This allows reducing anti-Parkinson medication, thus minimizing the medication-related side effects. Similar motor improvement can be obtained with DBS of the GPI, and the two procedures are currently in a phase of direct comparison. Available data suggest a superiority of STN stimulation in suppressing motor symptoms in the off medication state, while the relative incidence of cognitive and psychiatric side effects is still under debate.

Anatomical and neurophysiological data suggest that the dorso-lateral portion of the STN has sensory-motor functions, while the ventro-medial portion is involved in affective and limbic functions. The close vicinity of these areas could explain the observed incidence of cognitive and behavioural side-effects after STN DBS.

Even the most advanced neuroimaging techniques are only able to provide approximate clues to the position and borders of the target structure. Intraoperative microelectrode recordings are helpful in identifying the borders of the STN by detecting the neurophysiological signature of the nucleus with respect to surrounding areas. More sophisticated MER analysis would be needed to identify functionally distinct areas within the STN, e.g. the sensory-motor part and the limbic-associative part, or even areas related to distinct symptoms, such as tremor or bradykinesia.

4. DBS for Dystonia
Dystonia is defined as a syndrome dominated by sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. Dystonia can be defined as primary when no cause can be identified or a genetic cause is present and secondary when it occurs in the context of other neurodegenerative disorders, as a consequence of brain structural damage, or use of medications. While in secondary forms of dystonia other
symptoms can be present (e.g. ataxia or spasticity), in primary cases dystonia is usually the only neurological symptom. In some specific forms, named Dystonia plus syndromes, dystonic symptoms can be associated to other movement disorders, such as myoclonus in Myoclonus-Dystonia.

GPI DBS for dystonia has been introduced as alternative options for patients who are refractory to medical treatment. GPI stimulation is effective in reducing the motor symptoms and the associated pain in primary dystonia, and produces an improvement of functioning. Results of GPI DBS are different for different dystonic syndromes. In general, primary forms seem to respond better than secondary forms, partly because GPI DBS does not improve the other associated symptoms (e.g. ataxia or spasticity). It is not completely clear which secondary forms would benefit from GPI DBS and to which extent. Due to the lower prevalence of dystonia, the number of patients qualifying for surgery is smaller than those with PD. As a consequence, the scientific community is slowly building up experience and producing evidence concerning the spectrum of improvement and potential specific side effects associated with this procedure, which applies especially for the less common forms of dystonia, such as the Dystonia Plus syndromes. Particular attention should be given to psychiatric comorbidity: dystonic patients might have a higher risk of psychiatric symptoms such as anxiety or depression associated with their clinical condition. In these cases it is important to know whether GPI DBS increases the risk of occurrence or deterioration of existing psychiatric features.

4.1 Alternative surgical options
Other surgical options are available for the treatment of focal dystonia. These imply the peripheral resection of nerves or nerve roots, or muscle resection. The most commonly performed procedure among these is Selective Peripheral Denervation (“Bertrand procedure”). Early papers have reported extremely good results, however, the effect of this procedure has never been tested in controlled trials, and most reports date back to the times when BoNT was not available.

5. DBS for ET
ET is defined by the presence of tremor of arms or hands during posture or voluntary movements (“kinetic tremor”). Tremor may also occur in the head (neck), jaw and voice as well as other body regions. Stereotactic ablation and stimulation of the nucleus ventralis intermedius of the thalamus (Vim) effectively suppress tremor. However, outcome of surgery for ET is variable: while some patients have satisfying and long-lasting benefit, others have only partial or temporary benefit. This variability in clinical outcome might be due to differences in the position of the lesion (or electrode) or to inter-individual differences in the location of the tremor-related areas. Alternative targets have been proposed also for the treatment of tremor,
with different results. These include brain nuclei either within the thalamus (ventro-oralis anterior (Voa), ventro-oralis posterior (Vop)) or outside the thalamus (Zona Incerta, Forel fields, Posterior Subthalamic Area, Subthalamic Nucleus). Pre-operative non-invasive identification of tremor-related areas for each individual patient might help surgical teams refining their stereotactic target.

6. Current shortcomings of DBS
Nowadays, DBS for movement disorders is considered a routine procedure, although it still requires advanced technical equipment, specific surgical skills, and a complex multidisciplinary approach. The benefit provided by DBS on motor symptoms of PD, dystonia and ET is in many cases robust and long-lasting. However, after the original enthusiasm, the growing number of patients operated on and deeper insight reached through the analysis of the results have revealed also the shortcomings of this treatment. At least in some patients, effect can be partial or temporary, and the occurrence of surgical complications or stimulation-induced side effects can undermine the overall effect of the intervention. Reasons for unsatisfying effect could arise at different steps of the procedure, including the selection of patients, the choice of the appropriate kind of surgery and brain target, the accuracy of the surgical procedure, and the postoperative management. Moreover, technical issues might also prevent from obtaining optimal results. While most of the above mentioned issues are encountered irrespective of the clinical condition that is treated, other aspects are specific for the different indications.
AIM AND OUTLINE OF THIS THESIS

The work presented in this thesis covers some of the issues that are involved in the successful outcome of surgical treatment for movement disorders, by exploring possible strategies of improvement.

This thesis is organized in 4 parts.

**Part I: general issues concerning the accuracy of the Deep Brain Stimulation (DBS) procedure**
In this part factors are analysed that can induce the postoperative shift of DBS electrodes from their original position, such as subdural air invasion and subsequent resorption (chapter 2) and the use of different DBS electrode anchoring techniques (chapter 3).

**Part II: Parkinson’s disease**
In this part results are presented of qualitative frequency analysis of microelectrode recordings, aimed at investigating the association of tremor with a specific pattern of neurophysiological activity (chapter 4), or the effect of a prior pallidotomy on the neuronal oscillatory activity in the ipsilateral and contralateral subthalamic nucleus (chapter 5).

**Part III: Dystonia**
This part describes the role of patients’ selection (chapter 6), and the risk of psychiatric side effects (chapter 7) as determinants for the outcome of DBS of the Globus Pallidus pars interna for different kinds of dystonia. In chapter 8 we describe the role of alternative surgical techniques (selective peripheral denervation).

**Part IV: Essential tremor**
This part deals with refinement of the target for stereotactic surgery for Essential Tremor. In chapter 9 we present the Posterior Subthalamic Area (PSA) as a possible alternative target in a patient refractory to stimulation of the nucleus ventralis intermedius of the thalamus. In chapter 10 we explored the role of a new imaging technique that combines functional MRI and electromyography (EMG-fMRI) for the analysis of brain regions related to tremor in patients with Essential Tremor.
A general discussion is provided in chapter 11.
**REFERENCE LIST**

Chapter 1


