Improving surgical treatment for movement disorders
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Citation for published version (APA):
Contarino, M. F. (2013). Improving surgical treatment for movement disorders

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Chapter 11

Discussion
Deep brain stimulation (DBS) is a valid treatment alternative for all patients with movement disorders who present with an unsatisfactory response to medical treatment.\textsuperscript{1} The motor benefit provided by DBS on motor symptoms of Parkinson’s disease (PD), essential tremor (ET) and dystonia is often striking.\textsuperscript{1-3} However, the effect of DBS is sometimes far from optimal in some patients. Reasons for unsatisfying results should be sought at different stages of the procedure.

The work presented in this thesis investigates several aspects of the DBS procedure for different movement disorders, which may be important in determining the success of the treatment and that can still be further improved upon.

1. Patients selection

One of the most important determinants of surgical outcome is patients’ selection. DBS surgery does not produce the same effect in all patients. Important for the clinicians who pose the indication for DBS, is the ability to evaluate the expected benefit and the subjective risk of complications and side effects for the individual patient beforehand.

1.1 Expected benefit

The expected benefit varies in different forms or subtypes of the diseases, or for patients operated on in different stages of the disease. For example, patients with forms of Parkinsonism other than PD do no respond to DBS.\textsuperscript{4} As another example, dopamine-resistant symptoms have been shown to be resistant to STN DBS in PD, and therefore PD patients whose functional disability is mainly based on these symptoms could have a disappointing outcome.\textsuperscript{5} The issue of patient selection is even more intriguing in the field of dystonia, as this term includes a quite large variety of syndromes. In chapter 6 we reviewed the literature on DBS outcome in different forms of dystonia. The results of this review show that patients with primary dystonia generally have better results than patients with secondary forms of the disease. Interestingly, among the different forms of secondary dystonia, outcome can range from good to poor. The reason for this variability in outcome needs to be further investigated. One possible explanation is that other neurological symptoms, such as ataxia or spasticity that are often present in secondary dystonia, are not improved by DBS. When these symptoms account for the majority of the functional deficit, result of surgery is less satisfactory for patients and their families. Another explanation could rely on the progressive nature of some neurodegenerative disorders responsible for dystonia, as compared to the single-event nature of other conditions, such as post-ischemic dystonia. An accurate diagnosis and characterization of the disease is thus mandatory for an appropriate evaluation of the expected benefit.
1.2 Expected complications rate

Complications and stimulation-related side effects might occur after surgery. Depending on the nature and severity, these side effects can compromise the perceived benefit of an otherwise successful surgery. This is often the case in cognitive and psychiatric side effects, which have been observed in PD patients after STN DBS.\(^6,7\) Especially the increased rate of suicide after surgery has been a matter of worry.\(^8\) Worldwide experience with dystonia patients undergoing DBS is restricted in numbers, and therefore, less is known about the psychiatric side-effects or rate of suicide, especially for the less common forms of dystonia such as Myoclonus Dystonia (MD). In **chapter 7** we have reported that psychiatric side effects can occur also after GPi DBS for dystonia. Patients presenting pre-operatively with psychiatric traits or having a history of psychiatric disorders probably have an increased risk of developing psychiatric complications after surgery. Since these complications can be severe, it is crucial to perform an accurate psychiatric preoperative screening of patients undergoing DBS.

2. Choice of surgery

DBS is nowadays the surgical treatment of choice for movement disorders. Other options are however available and could be taken into account in selected cases.

2.1 Ablative stereotactic procedures

Ablative stereotactic procedures are nowadays rarely indicated because they are less effective than DBS.\(^3,9\) However, advantages include the lower costs and less complex post-surgical management. Ablative procedure could be proposed, for example, in patients with an unilateral non-progressive disorder, or for patients with logistic difficulties to visit a DBS centre for the mandatory follow-up, and in developing countries due to economic constraints.

2.2 Peripheral denervation procedures in dystonia

For cervical dystonia, non-stereotactic peripheral surgical options are also available. Selective peripheral denervation (SPD) has been performed in large groups of patients in the past, with excellent reported results. One obvious advantage of this procedure is that it does not require brain surgery, thus avoiding the risk of haemorrhage, stimulation-induced side effects and cognitive and psychiatric complications. The idea of an extra-cranial procedure is often more appealing for patients. We have shown in **chapter 8** that results of this kind of surgery, although satisfactory for some patients, can actually be considered inferior to GPi DBS, with many patients with SPD needing a second surgical procedure to keep the original benefit. We have also seen that the incidence of complications and side effects is actually larger for this surgery, even if the nature of these adverse events is milder than with GPi DBS. Therefore, in our experience GPi DBS is generally a better choice than peripheral
denervation, although the latter could still be a good alternative, for example for patients who have contraindications for DBS or when DBS is not available.

3. Refinement of stereotactic target
For stereotactic procedures, there are potentially several deep brain targets that could be chosen. In the history of stereotactic surgery for PD, some targets have been almost abandoned, such as the thalamus that is only effective on tremor, while others, such as the pedunculopontine nucleus or the Zona Incerta are still under evaluation. Currently, a strong debate concerns direct comparison between STN and GPi. Results coming from randomized trials show that effects of both nuclei are largely comparable, although a slightly different profile of effect could support the use of one or the other target. For dystonia surgery, GPi is currently the preferred target, although preliminary data on STN stimulation anticipate that comparative studies will be needed in this field as well. For ET, the thalamic Vim has for long been the target of choice. Lesion and stimulation of the Vim are usually quite effective in suppressing tremor, although results are not always complete and long-lasting. We present in chapter 9 the illustrative case of a patient with ET, who appeared unresponsive to Vim stimulation. Our case showed that Posterior Subthalamic Area could be used as alternative target for patients who are unresponsive to Vim. Other brain structures along the cerebello-thalamic circuit could also be considered as potential alternative target for the suppression of tremor. Unfortunately, at the moment it is not possible to predict which patients will effectively respond to Vim stimulation and which patients will not. Moreover, the currently available imaging tools are not able to directly visualize the Vim. This means that, at present, targeting is done in an indirect way that cannot take into account anatomical variability in the single patients. Even for those structures like STN or GPi for which direct targeting is possible based on MRI, imaging does not provide any functional information. In chapter 10 we explored the possible role of an innovative functional imaging method as an adjuvant tool for targeting. Combined EMG with functional MRI, was never tried before in patients with ET, due to technical obstacles. We managed to obtain clean recordings in a group of patients treated with thalamotomy for ET, showing the possible applications and the potential usefulness of this technique. More work needs to be done to refine the technique, but if successful, this could become a good support tool to supplement our current anatomical targeting with functional information.

Functional information is also sought during surgery by means of intraoperative MER. MER are nowadays used as a reliable tool to confirm and refine targeting of the STN, as they can easily identify the borders of the target nucleus. This information confirms and supports the anatomical targeting. An important next step is an instrument that can help refining the functional target even within the same nucleus. Cognitive and psychiatric side effects are thought to be a consequence of the close vicinity of circuits within the STN. More accurate and specific targeting might reduce the occurrence of postoperative side effects. We have
explored this potential role of the MER in chapter 4, where we showed that MER are able to distinguish tremor-related areas from others. This information can be used in the future not only to avoid side-effects related areas, but also to tailor surgery to the single patients.

4. Postoperative management

4.1 Technical issues
Some factors occurring postoperatively can undermine the outcome of an otherwise successful surgery. One assumption of stereotactic surgery is that optimally placed electrodes will not move from their original position. Some of our patients presented an insufficient effect of stimulation, even after successful placement of the electrodes, as confirmed by intraoperative testing. In other cases, loss of an initial benefit was observed. We have demonstrated that this might be due to postoperative electrode displacement (chapter 2). This observation points out the need of standard postoperative confirmation of the electrode position. Some technical factors might be responsible of postoperative electrode displacement: we have shown that improving the surgical technique can substantially reduce the impact of these factors. For example, large subdural air collections might induce a brain shift. In chapter 2 we showed that this factor directly correlates with the amount of electrode displacement. Air can invade the subdural space following CSF loss. Minimizing CSF loss, for example by sealing the burr-hole during surgery with fibrin glue, would therefore reduce the volume of subdural air collection, thereby minimizing brain shift and the consequent electrode displacement. In chapter 3 we have shown that this is indeed the case. After we modified our surgical technique, air invasions were minimal and were not a major contributor to postoperative electrode displacement anymore. Another important factor is the way electrodes are anchored to the skull. Several methods have been used in the past. Some of them were abandoned due to obvious inefficacy or to the possibility of damaging the electrode itself. For a number of years we used a simple custom-made method, based on the use of a titanium micro-plate. Later on, a more sophisticated technique based on a system with a plastic cap has become available. The fixation by micro-plate is still preferred by many implanting teams worldwide, due to the substantially lower costs. In chapter 3 we have shown that electrodes anchored with the titanium micro-plate had a significantly higher chance of migration in comparison to electrodes anchored with the new plastic cap, suggesting that implementing this new technique in clinical practice would reduce the amount of migrated electrodes and thus improve the outcome of surgery.

4.2 Clinical aspects
A good outcome of surgery is always based on the combination of a sizable benefit in the absence of complications or side effects. In chapter 7 we showed how this could be the case in a form of dystonia plus, myoclonus dystonia (MD). In our patients with MD who underwent GPi DBS, the effect on motor symptoms was striking. However, the motor benefit was not
always appreciated due to the occurrence of psychiatric side effects, or deterioration of pre-existing psychiatric conditions. The aim of any treatment should be improving the overall quality of life which cannot be restricted to motor aspects only. A thorough preoperative screening, and the availability of a psychiatric team to support patients after surgery, is thus recommended. This indicates once more the importance of a multidisciplinary approach to this type of surgery.

5. Insight into the pathophysiology of movement disorders
Our current knowledge and understanding of the functioning of basal ganglia and of the pathophysiology of movement disorders is clearly still fragmentary. In addition to offering a valid therapeutic option, stereotactic neurosurgery offers also a unique chance to investigate the functioning of basal ganglia circuitry and the pathophysiology of movement disorders. Intraoperative MER can be used to gather insight into the functional microanatomy of the subthalamic nucleus by identifying functional areas related to specific symptoms of the disease (Chapter 4). The evidence that an ipsilateral pallidotomy produces a modulation of the activity of neurons in the motor part of the STN (presented in chapter 5) offered new insights into the functioning of the basal ganglia. Based on these findings, we could hypothesise the presence of an excitatory connection from GPi to STN, although this has never been shown in anatomical studies. Alternatively, these results may indicate that the GPi influences the STN via multi-synaptic paths through the pedunculopontine nucleus or the thalamo-cortical loop. These hypotheses challenge the current models and suggest that more complex interactions might be present in the basal ganglia circuitry. New insights in the pathophysiology of movement disorders can also be reached with the help of innovative functional imaging techniques. In chapter 10 we explored how EMG-fMRI can provide information about the pathophysiology of ET. Our results suggest that the pathological activity in the cerebellum is independent and continuous, while thalamus activity is related to the task that induce tremor. This supports the hypothesis that different mechanisms are involved in the generation, execution and modulation of tremor in different brain areas.

6. Conclusion
Surgical treatment, and especially deep brain stimulation, has changed the life of many patients with movement disorders. The outcome of this valuable technique is still not optimal. A continuous critical evaluation of the growing amount of clinical data should lead to the identification of aspects that may improve the procedure. In addition, through a minimally invasive procedure, deep brain stimulation opens a privileged perspective to learn more about the fascinating world of the basal ganglia functioning and the pathophysiology of movement disorders. This increased awareness will ultimately contribute to further improving of the treatment of our patients.
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