Summary
The medical treatment of patients with Parkinson’s disease (PD), dystonia and essential tremor (ET) is often unsatisfactory. For these patients, stereotactic neurosurgical treatment can be a valid alternative. Stereotactic Deep Brain Stimulation (DBS) is a well-accepted and widely performed treatment nowadays.

The benefit provided by DBS on motor symptoms of PD, ET and dystonia is in many cases robust and long-lasting. However, effects can be partial or temporary, at least in some patients, and the occurrence of surgical complications or stimulation-induced side effects can undermine the overall benefit of the intervention.

Reasons for unsatisfying effect could arise at different steps of the procedure, including the patients’ selection, the choice of the appropriate kind of surgery and brain target, the accuracy of the surgical procedure, and the postoperative management. Additionally, technical issues might also prevent from obtaining optimal results.

The focus of this thesis is on the improvement of several unsolved issues in the surgical treatment of movement disorders.

This thesis is organized in 4 parts. A general introduction is provided in chapter 1, which provides an overview of the neurosurgical treatment of movement disorders, an explanation of the techniques and applications of DBS, as well as a brief discussion of problems associated with the surgical treatment.

Part I: general issues concerning the accuracy of the DBS procedure

In this part factors are analysed that can induce the postoperative shift of DBS electrodes from their original position. One of these factors is cerebrospinal fluid (CSF) loss and consequent subdural air invasion (chapter 2). By means of image co-registration of immediate postoperative computer tomography (CT) and follow-up CT with pre-operative stereotactic MRI, we showed that the brain shift associated with subdural air resorption causes an upward displacement of DBS electrodes that is proportional to the amount of air entering the skull during surgery. CSF loss can be minimized by improving the surgical technique. Changes include planning the burr holes on top of a gyrus, performing surgery with patients in a semi-sitting position and, in particular, effective sealing of the burr hole with fibrin glue immediately after introduction of the microelectrodes and macro-stimulation electrode. As we showed in chapter 3, by applying all the above mentioned improvements, subdural air invasions are reduced and are not a major determinant of postoperative electrode displacement anymore. Among other factors that might still influence postoperative electrode shift, we only found a significant association with the method of anchoring DBS electrodes: displacement was larger for DBS leads anchored with a titanium micro-plate. Although micro-plates are less expensive, the commercially-available plastic cap system is more efficient in preventing postoperative DBS electrode displacement.
Summary

Part II: Parkinson’s disease
This part presents the results of qualitative frequency analysis of microelectrode recordings (MER) in different areas of the subthalamic nucleus (STN). In chapter 4 we showed the association of tremor with a distinctive neuronal oscillations pattern. In particular, we demonstrated the specificity of the association of theta frequencies (3-8 Hz) measured in the dorsal STN with tremor. A difference between dorsal and ventral STN characterizes also neurophysiological changes that occur after an ipsilateral pallidotomy. In chapter 5 we show indeed that pallidotomy suppresses beta power (13-30 Hz) predominantly in the dorsal part of the ipsilateral STN. This finding is also interesting because it challenges the current model of basal ganglia circuitry and suggests the presence of more complex modulatory interactions in the basal ganglia.

Part III: Dystonia
The term dystonia is common to a number of different syndromes, including primary and secondary forms, and “dystonia plus” syndromes. Deep brain stimulation has been performed in many of these syndromes, with varying results. This variability in outcome could be associated with the nature of the underlying disease. In chapter 6, we have reviewed the literature concerning 341 patients with primary and 109 with secondary dystonias, who were treated with DBS of the internal segment of the Globus Pallidus (GPI). In general, the outcomes for primary dystonias were more favourable compared to the secondary forms, although also for some secondary dystonias outcome was still satisfactory. This suggests that especially for secondary and “dystonia plus” syndromes, a case-by-case evaluation should be performed, taking into account the disease characteristics and the determinants of functional disability for each patient. A good clinical outcome is not only related to motor benefit but also to minimization of post-operative side effects. This is especially true for cognitive and behavioural side effects. In chapter 7 we have shown that the onset of psychiatric symptoms or the deterioration of pre-existing psychiatric conditions can occur after GPI-DBS for myoclonus-dystonia. This can affect quality of life of the patients after surgery, even in the presence of an excellent motor improvement. Systematic preoperative evaluation of psychiatric comorbidity, and close post-operative follow-up are thus recommended in all DBS patients.

In patients with cervical dystonia (CD), symptoms are confined to the neck. If no satisfactory improvement is achieved with botulinum toxin treatment, surgery may be considered. In the past, a peripheral denervation of neck muscles (Bertrand’s surgery) was performed. This has been recently replaced by GPI-DBS. Cognitive and psychiatric side effects, as well as intra-cerebral haemorrhage, are not a risk of peripheral neurosurgery. For this reason, peripheral techniques, such as selective peripheral denervation for cervical dystonia, could meet patients’ preference if the benefit provided is comparable.
We retrospectively explored our data on patients with cervical dystonia (CD) who underwent selective peripheral denervation or GPi-DBS in order to compare outcomes of these procedures (Chapter 8). Based on our data we suggest that GPi-DBS produces larger benefit than selective peripheral denervation in CD patients unresponsive to botulinum toxin treatment. DBS is potentially associated with more severe complications and side effects; present-day procedure however, carries a low overall risk while selective peripheral denervation is associated with a higher rate and permanent nature of side effects. Selective peripheral denervation could be offered in selected cases, in consideration of the individual risk profile. The choice of surgery should be thoroughly discussed with the patient, in light of all available evidence.

Part IV: Essential tremor
In this part we investigated the refinement of target for DBS for ET. In chapter 9 we presented the Posterior Subthalamic Area (PSA) as a possible alternative target for patients who are refractory to Vim stimulation. In chapter 10 we explored the role of a new imaging technique which combines functional MRI (fMRI) and electromyography (EMG-fMRI) for the analysis of brain regions related to tremor in patients with ET. We could show an association between tremor and activity in the ipsilateral cerebellum and contralateral thalamus detected by EMG-fMRI. However, the activation spot in the thalamus varied across patients and did not correspond to the thalamic nucleus ventralis intermedius, which is the target of choice for serotactic surgery for tremor. Thus, while being an interesting tool to explore the pathophysiology of tremor, this technique must be further developed before being useful in supporting targeting for stereotactic surgery.

A general discussion is provided in chapter 11. We conclude that a continuous effort should be made to critically review our experience with surgical approaches for movement disorders and to try to improve the remaining issues in order to further optimize the outcome of these procedures. In addition, 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.