Selective stimulation of the subthalamic nucleus in Parkinson’s disease: dream or near future

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Parkinson disease is a progressive neurodegenerative disorder. In Europe 108 out of 100,000 people suffer from Parkinson disease. The key motor symptoms are tremor, rigidity, bradykinesia and postural instability, also non-motor symptoms such as cognitive impairments and mood changes appear. Parkinson disease is neuropathologically recognized by loss of dopamine cells in a specific part of the brain and the presence of Lewy bodies (a misfolded protein). In the early stages of the disease motor symptoms can be adequately improved by oral dopamine drug replacement therapy. Unfortunately, the beneficial effects wear off progressively and ‘on-off’ fluctuations and L-dopa induced dyskinesias appear. In this stage of disease deep brain stimulation is the first choice therapy. Since the introduction of deep brain stimulation of the subthalamic nucleus in 1993, this therapy has proven to be effective on the short and long term. However, in a substantial number of patients neuropsychiatric side effects are seen. In this thesis we investigated the pathophysiological mechanisms of these side-effects and tried to overcome these by pre-clinical experiments in an animal model of Parkinson disease and by an electrophysiological approach in Parkinson patients during deep brain stimulation surgery.

In the first chapter of this thesis we show the short and long term outcome of subthalamic nucleus deep brain stimulation in our cohort of patients. We learned that some neuropsychiatric symptoms are present in some patients. We have seen an increased impulsivity in younger patients, whereas general cognitive problems were seen in older patients. As reported in literature we also have seen deterioration in gait after 10 years. This chapter shows that the issues raised in the international literature are also present in the Dutch population and therefore in need for further studies to overcome these problems.

In chapter 2 we investigated the behavioral side-effects in a rodent. We used a widely used model for Parkinson disease, namely the 6-OHDA model. We found behavioral deficits which are related to the serotonin system, which is involved in depression. Next we tested the connection between the subthalamic nucleus and the dorsal raphe nucleus, a brainstem region in which serotonin is produced. We found changes using immuno-histochemical markers, which underline the fact that deep brain stimulation of the subthalamic nucleus affects the serotonin system. This finding led to further scientific investigations in animal models as well as in Parkinson patients and might be a first step in overcoming depressive symptoms induced by subthalamic nucleus stimulation.

In chapter 3 a review of the literature was performed to investigate the cortical connections with the subthalamic nucleus. The findings of this literature review were necessary for the experiments in chapter 4 and 5.
In chapter 4 we tested deep brain stimulation in certain brain areas in animals to treat depression. The mechanism behind the efficacy of stimulation of these areas is still not fully understood. Since the STN is also connected to these areas we investigated which part and to what extend the STN is involved. The findings of this experiment help the scientific community to understand the mechanisms behind the efficacy of deep brain stimulation in depression and might in the end lead to novel therapeutic options for depressive patients.

In chapter 5 we tested if the subthalamic nucleus has three independent subdomains with different functionality. We tested this using an electrophysiological approach in an animal model. We learned that there is a partition seen, but overlap is present. This finding has clinical implications for deep brain stimulation of the subthalamic nucleus in Parkinson patients. Pure selective stimulation to reduce motor symptoms without inducing undesired behavioral side effects might thus not be possible. This has direct consequences for these patients.

In chapter 6 and 7 we aimed to overcome undesired side-effects of deep brain stimulation of the subthalamic nucleus in Parkinson patients by applying stimulation of the superficial brain region which corresponds with motor function. This technique was promising and if the responses acquired would have been clearer, it would have been possible to further improve the motor symptoms without inducing undesired behavioral side-effects. This would have reduced medical costs significantly.

In chapter 8 we assessed a novel tool to assess gait in an animal model of Parkinson disease. Gait as shown in chapter 1 is a major problem in patients with advanced stages of Parkinson disease. Thus far no therapies are available to treat this symptom. Falls lead to hospital admissions and hip-fractures. This study was necessary to be able to further investigate gait problems in animal models to be able to develop novel therapies for the gait disturbances. If a treatment can be developed this leads to lesser burden for the patients and caregivers, as well as a reduction in medical costs.

In chapter 9 we performed a basic scientific experiment which helps us to understand the pathophysiology in Parkinson disease. The results of this experiment contributed to the basic knowledge of the scientific community.

In summary, the experiments performed in this thesis consisted of clinical experiments with patients, experiments with animal models and a review of the literature. The scientific approaches used were well reasoned. The approaches chosen depended on the research question which needed to be answered. Although we are aware that the trans-
lation of animal data to humans is often difficult, animal research is indispensable to establish advances in neuroscience. In my opinion, not only clinical studies, but also pre-clinical experiments using animal models are thus necessary to sustain the high quality of our medical care and basic scientific knowledge. I therefore encourage the European and Dutch Government, as well as private funding programs to keep funding basic scientific research in which animal research is involved.