Exciting circuits

Deep brain stimulation for depression

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Chapter 1

Introduction

When I got involved in this Ph.D. project on the 15th of November, 2009, the scientific literature described 45 patients with depression who had undergone deep brain stimulation (DBS). DBS was applied as an effective treatment for motor disorders for more than 20 years, but only recently was it attempted as a last resort treatment in patients with depression. More than half of these 45 patients improved substantially after DBS, offering a glimmer of hope for patients who suffered from depressions which did not improve despite all available treatment options.

These pioneering studies showed promising effects and preliminary evidence of the safety of the procedure. However, many questions remained to be answered: was the symptom improvement caused by DBS or a placebo effect? Which adverse events were associated with DBS? Did it have any effect on cognitive functions, such as memory, attention or executive functioning? Did it matter in what brain target DBS was applied or how DBS parameters were optimized? Could some variables predict who would and who would not improve after DBS?

In other words, studies were needed to learn more about the exact effects of DBS for depression. This project was one of the studies to help answer some of these basic questions. This thesis contains some of the answers.

1.1 Major depressive disorder

The patients we were going to treat were suffering from Major depressive disorder (MDD), who did not respond to available treatments. MDD is a psychiatric disorder, defined as the presence of a depressed mood and/or a substantial decrease of everyday interests. It is accompanied by at least three of the following symptoms: 1) decreased or increased appetite; 2) insomnia or hypersomnia; 3) psychomotor retardation or agitation; 4) loss of energy; 5) feelings of guilt; 6) loss of concentration or decision making; or 7) recurrent suicidal ideation. Patients suffer from these symptoms (almost) every day for most of the day.

These symptoms result in substantial loss of quality of life and often to a decreased ability to work. On a societal level, MDD leads to high costs, given the loss of productivity and the intensive health care utilization. Further-
more, it is a highly prevalent disorder with approximately 15% of the population in high-income countries suffering from at least one depressive episode during life. Effective treatments range from different forms of psychotherapy, to antidepressants and electroconvulsive therapy (ECT). Unfortunately, as many as 30% of the patients do not respond to four consecutive treatments.

1.2 Treatment resistance

Different definitions of treatment-resistant depression (TRD) exist, but most authors propose staging methods with patients unresponsive to more treatments getting designated a more advanced stage of TRD. For instance, the Thase and Rush Staging Model defines one failed antidepressant as Stage I and four failed antidepressants plus a failed ECT series as Stage V treatment resistance. In our DBS study, patients had to have failed at least five different antidepressants and ECT, and, therefore, would be classified as the most advanced stage of TRD. These patients are usually treated with a combination of maintenance pharmacotherapy and psychotherapy, or in rare cases with maintenance ECT. In case of substantial residual symptoms, it is advised to start a rehabilitation program. Most patients with such an advanced stage of TRD will suffer from depression for the rest of their lives and many become suicidal. Approximately 30% of TRD patients attempt suicide at least once in their lives.

1.3 Deep brain stimulation

In 2005 and later in 2008, hopeful articles were published, in which TRD patients were treated with DBS. DBS consists of the placement of electrodes in specific brain areas, which are connected to a neurostimulator. The neurostimulator produces a continuous stream of electric pulses, which modulate brain tissue around the electrodes. Specific parameters can be adjusted to optimize efficacy and to minimize side effects. For instance, increasing voltage increases the area of modulated tissue.

In the first report, four out of six patients lost at least half their symptoms after DBS targeted to the subcallosal gyrus (SCG). A later report extended these results, showing 12 of 20 patients responded after one year of SCG DBS. The SCG was chosen on basis of its dense connections with other brain regions, its increased activation in depressed patients compared to controls and the decrease in activation after an effective antidepressant therapy.

Another group considered the nucleus accumbens (N.Ac.) and adjacent internal capsule as a potential DBS target. This was chosen based on its central
role in the reward circuitry and the possibility to modulate extensive network functioning given its many afferent and efferent projections.\textsuperscript{184} Two of the first three treated patients responded and showed a relapse when the stimulator was turned off.\textsuperscript{188} Another group corroborated these findings in a slightly different target: 8 out of 15 patients responded to stimulation of the ventral striatum and surrounding capsular area.\textsuperscript{124}

For this Ph.D. project, we chose the N.Ac. and adjacent internal capsule as a target. This was based on the promising results described above,\textsuperscript{124,188} as well as the clinical experience of our team. At that time, our team followed 16 patients with obsessive-compulsive disorder (OCD) treated with DBS, who experienced a robust and substantial effect on mood preceding the effect on OCD symptoms.\textsuperscript{51} The target is described as the ventral anterior limb of the internal capsule (vALIC), given active contact points are almost always located in that area.\textsuperscript{214}

1.4 Effects on cognitive functions

Although the clinical results of only 45 patients were described in 2009, this was a wealth of information compared to what was known on the effects of DBS on cognitive functions: results of only seven TRD patients after DBS had been reported.\textsuperscript{94,136} In none of these patients a pattern of consistent cognitive decline was noted, so preliminary results pointed towards DBS being safe from a cognitive perspective. However, seven patients are not enough to draw reliable conclusions.

Cognitive outcome deserves attention, given DBS leads to cognitive declines in a substantial subset of patients with Parkinson’s disease.\textsuperscript{198,227} Furthermore, major depression is associated with cognitive deficits,\textsuperscript{173,215} which in turn are associated with problems in everyday functioning.\textsuperscript{42,76,133} It is, therefore, of the utmost importance that antidepressant treatments do not result in further decline.

1.5 Overview and specific questions

The scarcity of research on DBS for depression led to the general aim of this project: is DBS of the vALIC effective for depression? Additionally, we were interested in the safety of DBS, with a focus on cognitive functions. This resulted in a project with two major themes: efficacy and safety.

In Part II, we explore questions of efficacy. In Chapter 2, the most basic question of every new treatment is investigated: is DBS effective in reducing depressive symptoms of TRD patients? We carried out a clinical trial, in which we treated TRD patients with vALIC DBS for one year. In a randomized, dou-
ble blind crossover phase, we explored whether the effect could be attributed to the stimulation or placebo. Chapter 3 focuses on the importance of diagnostically screening and a possible predictor for non-response by discussing the case of Mrs. A, who responded to exposure therapy after DBS had failed to relieve her symptoms.

In Part III, the safety of DBS is explored. In Chapter 4, we zoom in on the high suicide risk of TRD patients and whether DBS or any other treatment increases or decreases this risk. To this end, we meta-analyzed the rate of attempted and completed suicides in TRD patients following the initiation of different treatments. In Chapter 5, we summarize the literature on cognitive functioning after DBS in psychiatric disorders. We then contribute to this literature in Chapter 6 with a study on the effects of DBS on basic cognitive functions, controlling for practice effects by following a group of healthy volunteers. We also directly compare cognitive results following active DBS compared to sham DBS. Finally, in Chapter 7, we turn to the more complex cognitive function of autobiographical memory. We compare the decline of autobiographical memories over time between healthy volunteers, patients treated with DBS and patients treated with ECT.

In Part IV, we integrate the studies described in this thesis with those done in the rest of the world during the same period. We discuss what we have learned on the efficacy of DBS, in what ways we can optimize the treatment, and the methods we use to evaluate treatment outcome. In addition, we discuss what we currently know about the effects of DBS on cognitive functioning of TRD patients, and the limitations and remaining gaps in the literature.