Exciting circuits

Deep brain stimulation for depression

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Chapter 8

General discussion

When I started working on this project late 2009, many questions on deep brain stimulation for depression needed answers. Some eight years later, this project and many others around the world helped to answer some of these. In this final chapter, I will link the findings of our studies to those in the rest of the world. Based on this synthesis, I try to answer what we have learned about the efficacy, safety and cognitive outcome of deep brain stimulation (DBS) for depression, and what questions are still left to answer.

8.1 Summary of main findings

8.1.1 Deep brain stimulation is effective for depression

In Chapter 2, we showed DBS of the ventral anterior limb of the internal capsule (vALIC) to be effective: 10 of the 25 included patients lost at least half and another 6 at least a quarter of their symptoms after one year of DBS. Our study was also the first to show patients suffered less from their symptoms during active than during sham DBS.

Despite these positive results, nine patients did not improve after DBS. In Chapter 3, the case of Mrs A. shows how careful diagnostic screening might improve treatment selection. After 17 months of testing DBS parameters without any relief of symptoms, it turned out Mrs A. suffered from posttraumatic stress disorder (PTSD). After turning DBS off and starting an intensive 2-week exposure therapy, her PTSD as well as her depressive symptoms went into remission.

8.1.2 Deep brain stimulation is safe

Although we identified a long list of adverse events (Chapter 2), these were mostly unrelated to the treatment, transient or disappeared after parameter adjustment. As in other DBS studies, we found transient (hypo)manic symptoms after initiation of stimulation and signs of mild disinhibition at higher voltages.

Four of the included patients attempted suicide during the first year of treatment (Chapter 2), raising the question whether DBS might impact suicidality. A meta-analysis of attempted and completed suicide incidences showed these
to be similar following deep brain stimulation, electroconvulsive therapy and vagal nerve stimulation (Chapter 4). We concluded TRD patients have a high suicide risk, but specific treatments do not increase this risk.

Deep brain stimulation is also (mostly) safe from a cognitive point of view. A review of the literature revealed DBS did not cause cognitive decline and several studies reported cognitive enhancement independent of symptomatic improvement (Chapter 5). Our own study found neither cognitive decline nor improvement following DBS on basic cognitive tests (Chapter 6). However, autobiographical memories declined faster over time in patients treated with DBS than in healthy controls, but less than in patients treated with ECT (Chapter 7).

8.2 Is deep brain stimulation effective for depression?

Our clinical trial (Chapter 2) continued a line of promising results of open label studies on DBS targeted to the subcallosal gyrus (SCG), and striatal and capsular areas. However, while our trial was running, two randomized controlled trials (RCTs) found no differences between active and sham DBS. In the first one, 3 of 15 patients (20.0%) in the active arm and 2 of 14 patients (14.3%) in the placebo arm showed a full response following four months of DBS of the ventral capsule / ventral striatum (VC/VS) - a different target, but close to the vALIC. In the other one, 12 of 60 (20.0%) in the active and 5 of 30 (16.7%) patients in the placebo arm showed a full response after six months of DBS targeted to the subcallosal gyrus (SCG).

These disappointing results have raised questions on the efficacy of DBS for depression. What factors might explain these differences in efficacy? What can we learn from these studies about targeting, parameter optimization and other factors involved in the treatment?

8.2.1 Targeting

The first, obvious factor to take into account is the targeting. In the earliest studies the SCG and nucleus accumbens (NAc) were targeted, because these nuclei showed aberrant activation in patients with depression and were densely connected with other brain areas. Direct modulation of these nuclei was hypothesized to normalize aberrant neuronal activity, which would change activity in downstream networks resulting in symptom decrease.

However, for both SCG and NAc stimulation the contacts with the most optimal clinical improvement turned out to be in white matter tracts and not in the nuclei themselves. For the SCG it has been located on a crossroad of the cingulum bundle and uncinate fasciculus, and for the NAc in the medial
forebrain bundle (MFB).\textsuperscript{38,39} A first analysis of the targeting in our group of OCD patients also shows symptom reduction is associated with proximity to the MFB.\textsuperscript{113}

Preliminary open-label trials suggest targeting these specific bundles instead of nuclei results might boost response. Not only does it result in response rates between 70 and 90\% in small samples, but also in a faster response with smaller areas of stimulated tissue.\textsuperscript{22,65,171,186} This work shows the huge potential of more specific targeting and expanding this to bigger samples should be the first step in future trials.

\subsection*{8.2.2 Parameter optimization}

Another important factor is the method of parameter optimization. The choice of polarity (bipolar or monopolar stimulation), amplitude (voltage), frequency and pulse width all affect how brain activity is modulated.\textsuperscript{30,217} For instance, the focus of bipolar stimulation is directly around the negative contact with minimal modulation of more distal tissue, whereas monopolar stimulation results in more widespread current distribution. Furthermore, amplitude controls the diameter of stimulated tissue and pulse width controls the type of axons stimulated. The importance of parameter selection is clear from studies in motor disorders. Monopolar and bipolar stimulation result in a similar tremor reduction, although bipolar stimulation might need higher amplitudes.\textsuperscript{8,50,156} Lowering the pulse width also might need marginally higher amplitudes to reach effective symptom reduction, but does lead to a wider therapeutic window.\textsuperscript{27,200} In addition, different frequencies might differentially affect symptom dimensions. Usually frequencies higher than 100 Hz are used, which result in a better motor outcome than lower frequencies. Some studies, however, indicate 60 to 80 Hz might have a similar or even superior effect on bradykinesia, rigidity, or freezing of gait.\textsuperscript{52}

Unfortunately, systematic exploration of effective stimulation parameters for depressive symptoms is rare. Dougherty et al.\textsuperscript{55} used bipolar stimulation unlike almost all other DBS studies in depression, which might indicate this is less effective than monopolar stimulation of striatal and capsular areas. Anecdotally, lowering the pulse width resulted in a decrease of agitation and restlessness while preserving the antidepressant effect, which suggests lower pulse widths might widen the therapeutic window (Chapter 2). In addition, a higher frequency (130 Hz vs 20 Hz) and longer pulse widths (270-450 vs 90-150 $\mu$s) were associated with more symptom reduction in 9 and 4 patients respectively.\textsuperscript{59,167} However, the many drop-outs in one,\textsuperscript{59} and the lack of control for order effects in the other study,\textsuperscript{167} plus the small number of patients do not allow generalization to a definite optimization paradigm.
Just as specifying targeting, identifying effective parameters should be another major focus of future work. This could be done by systematically manipulating parameters such as frequency or pulse width in patients who are on stable settings. An alternative method is selecting parameters based on a computer model of the expected stimulated tissue. Such a model led to lower energy intensities and faster response in patients with Parkinson’s disease compared with the traditional trial and error parameter selection. Until we have a firmer understanding of the effects of different parameter settings, it is advisable to keep the optimization paradigm flexible enough to test many different combinations to prevent suboptimal stimulation in future trials.

8.2.3 Other factors

Besides factors that change the nature of neuromodulation directly, many others play a role in the treatment outcome. Firstly, the factor of time should not be neglected. Not only does the clinician need enough time to test multiple combinations of DBS parameters, time itself might be pivotal in the patient’s recovery. Most patients do notice acute improvements after an effective DBS setting is found, like mood elevation, anxiety decrease, energy increase or more motivation to engage in activities and social interaction. At the same time, however, patients need to adjust their lives to these changes, such as finding new activities or social contacts. In addition, after the initial acute improvement, patients frequently show a mourning reaction when realizing many years of their lives have been lost to depression. In clinical practice, we have seen this often leads to a temporary deterioration of symptoms, which is also described in patients with TRD following SCG DBS.44 These factors suggest several months are needed to harness the full potential of DBS, even though some symptoms might decrease immediately. In OCD patients, adjustment to and coping with the changes following DBS is accelerated by cognitive behavioral therapy (CBT).125 CBT might improve the results in TRD patients as well, but so far this has not been tested in any study.

Another factor that would improve outcome is patient selection. Given the current small sample sizes, it is impossible to identify solid predictors for response. However, some have suggested longer episode duration as a predictor for poor or delayed response.84 Furthermore, specific comorbid diagnoses might predict poor outcome, as our patient with co-morbid posttraumatic stress disorder cautiously points to (Chapter 4). Others have used machine learning techniques to predict response following SCG DBS in a proof of concept study. They predicted response status of 20 patients with 90% accuracy based on a certain cognitive profile.134 To improve response prediction we need to systematically record a broad spectrum of baseline variables, which could in-
clude clinical, psychological, social, cognitive, neurobiological, immunological or somatic variables.

Finally, the method of measuring and defining response impacts the study outcome. From the earliest DBS studies on depression onwards, authors have argued the standard symptom scales do not capture outcome of TRD patients accurately as these disregard functional improvement and symptom fluctuations over time. Furthermore, the response criterion (>50% decrease of symptoms) might be unrealistic in a severe TRD population. To overcome these limitations, lowering the response criterion to 40% symptom decrease and analyzing response over an extended period of time have been proposed. These solutions, however, still neglect functional improvement independent of symptom improvement, which do not seem to overlap in a substantial minority of patients. In a survey amongst 503 depressed patients, around a quarter of patients judged themselves as being without functional impairment despite remnant symptoms and half of these even considered themselves to be in remission. This is in line with clinical observations in our trial. Several patients were satisfied with their improved daily lives despite being classified as a non-responder. On the other hand, some responders showed symptomatic and functional improvement, but felt purposeless because they struggled to form new life goals. This could be the consequence of a chronic disease course, but might also be associated with less detailed autobiographical memories (which is discussed below). These discrepancies between symptomatic improvement and functioning in everyday life might be better captured by quality of life scales. Other possibilities include semi-structured interviews to get a personalized view of experienced changes by patients, or using experience sampling method to get a day-to-day evaluation of activities and mood.

8.3 Is deep brain stimulation safe?

Most patients tolerated DBS well, since most adverse events were unrelated to DBS, transient or disappeared after parameter adjustment (Chapter 2). Frequently observed adverse events coinciding with parameter changes were restlessness, agitation, disinhibition and sometimes (hypo)mania. Other studies with DBS targeted to striatal and capsular areas found similar stimulation-dependent adverse events. Of note, only patients with active DBS experienced this type of adverse events and these also disappeared after lowering the amplitude. These convergent observations show DBS likely has an effect on behavioral inhibition. This is an adverse event needing close attention, but it might also be partly responsible for the positive effect of DBS. A moderate lowering of extreme inhibitions might be necessary to initiate and engage in activities. However, too much loss of inhibition might lead to agitation,
disinhibition or even (hypo)mania.

### 8.3.1 Suicidality

A point of concern is the high degree of suicidality: in the first year four patients attempted suicide (Chapter 2). This high rate is common in other DBS trials as well, although a preliminary exploration shows it is not significantly different from the rate found in TRD patients after ECT or VNS (Chapter 3). It is, however, a stern warning when designing new trials or implementing DBS as a treatment: DBS might not increase suicide risk, but this risk is extremely high in the eligible patients. Due care should be taken in managing suicidal ideation and accurately recording suicidality in these patients.

### 8.3.2 Basic cognitive functions

Until 2012, small and uncontrolled studies showed stable or improved cognitive functioning after DBS in depressed patients (Chapter 5). Similar results have been found by other uncontrolled studies after 2012. Some authors even suggested DBS could cause cognitive enhancement, because cognitive improvement was uncorrelated with symptom improvement. The lack of control groups or direct comparison of active with sham DBS, however, made it difficult to dissect practice from stimulation effects.

In our controlled cognitive study, we replicated DBS was safe considering basic cognitive functions. However, we did not establish cognitive enhancement, neither in the open-label phase nor by comparing active with sham DBS (Chapter 6). Other controlled studies also did not find cognitive enhancement. SCG DBS resulted in comparable improvements in those with and without SCG DBS over time. In addition, one sham-controlled study found mostly comparable cognitive change in patients after four months of sham or active VC/VS stimulation with one exception: patients with active DBS decreased on a measure of cognitive inhibition, whereas patients with sham DBS improved slightly. This last result is a warning to rule out any cognitive adverse events of DBS too soon.

In addition, all aforementioned studies have analyzed results on a group level, meaning stable cognitive functioning is found on average. This might overlook individual differences between patients, in which a subset of patients might improve and another might decrease. Analyses using reliable change indices (RCI) could capture clinically relevant changes of individuals over time. Several papers show a higher rate of patients with Parkinson’s disease show clinically relevant cognitive decline after DBS than after optimal medical treatment. Currently, only Bogod et al have used RCI to analyze cognitive outcome of DBS in depression. They did not find a consistent pat-
tern of decline on any cognitive function, but they followed only four patients. In sum, although most studies find stable cognitive functioning after DBS in depressed patients, the current level of evidence is mediocre at best. It is therefore, essential to increase the number of controlled studies to get a clearer picture of cognitive outcome following DBS. These studies should consider a broad range of tests and if possible, apply analysis methods on group- as well as individual levels. The importance of increasing the quality and quantity of cognitive studies is stressed by the state of cognitive research following ECT. In 2003, 65 years after the first ECT was done, the UK review group could not do a meta-analysis of cognitive functioning, because they identified only two controlled studies. Hopefully, a meta-analysis of controlled studies on cognitive outcome following DBS is possible in a decade or two.

8.3.3 Autobiographical memory

One of the tested cognitive functions did not show stable functioning in our sample of TRD patients: autobiographical memory. After surgery, autobiographical details of patients declined in a rate comparable to healthy controls. Following stimulation, however, the decline was faster than expected on basis of natural decline (Chapter 7). This is another warning to rule out cognitive adverse events of DBS too soon. Even though DBS might not affect learning of basic verbal and visual material (Chapter 6), it might affect more complex memory systems such as autobiographical memory.

Autobiographical memories are an essential part in forming a sense of self, which follows a more or less consistent path from the past to present. A consistent sense of self allows mental time travel to the future, closely linking autobiographical memories to future goals. Autobiographical memories of depressed patients are consistently found to lack in detail, which is referred to as ‘overgeneral’ autobiographical memories. Overgeneral memories have been associated with deficient future planning, less effective problem solving, more rumination, and more suicide attempts. Autobiographical memory training can reduce these consequences and has been associated with beneficial treatment outcome in depression.

Given the possible impact of DBS on autobiographical details, DBS might also worsen functions such as future planning and problem solving. For instance, the aforementioned sense of purposelessness despite symptomatic improvement might be a reflection of the inability to plan and maintain future goals. This makes autobiographical memory an extremely important topic to explore further. First of all, the impact of DBS on autobiographical memory needs replication. Second, the interview we used only asked about events in the last year before DBS surgery, so it is unclear whether the impact extends
to more remote memories. Furthermore, the relationship between DBS, autobiographical memory, sense of self, future planning and problem solving should be substantiated. If the reduced detail in autobiographical memories indeed are related to reduced future planning, treatment outcome might be enhanced with autobiographical memory training.

8.4 Overall conclusion

This project strengthens the claim that deep brain stimulation is an effective and safe treatment for depression and is a huge stimulant to set up new trials. These new trials can benefit from the insights gained over the previous years to improve outcome even further. More specific targeting, firmer knowledge on parameter selection and addition of psychotherapy are all likely to increase response rates. This project has been the first step on a promising road to a powerful new treatment, which offers new hope for the thousands who suffer from relentless depressions.