Neurosurgery in Obsessive Compulsive Disorder

Impact and valorization

In scientific research, there are two key types of relevance: scientific relevance, where a study increases our understanding of a disease or a process, and societal relevance, where society directly benefits as a result of this increased understanding.[1] Vice-versa, a main characteristic of the societal relevance of research is therefore the quest towards answering questions that society asks or to solve problems it faces.[2] Taken together, this thesis has both scientific and societal impact relevant to a broad target audience including, OCD patients, clinicians, psychologists and (clinical) researchers.

Societal Relevance – Closing the treatment gap

In the 2017 WHO report 'Depression and other common mental disorders' anxiety disorders, among which OCD, is listed as the sixth largest contributor to non-fatal health loss globally, with a global 24.6 million Years Lost to Disability (YLD, defined as the number of years with a lower quality of life due to the disease). From a national perspective, this report estimated the prevalence of anxiety disorders to be 6.4% (1 024 103 of total cases) in the Dutch population with a disease burden of 93.907 YLD (5.3% of total YLD). Given the estimated lifetime prevalence of OCD of 0.9% in the Netherlands, a rough estimation of OCD specific disease burden can be extrapolated to 13.205 YLD.[3]

If patients fail to respond to CBT, two SSRI trials, clomipramine augmentation and additional therapy with antipsychotics, they can be considered treatment refractory. It is estimated that approximately 40-60% of the patients remain treatment-refractory, commonly defined as a less than 25% reduction on the Y-BOCS.[4] For these patients, neurosurgery (GVC or DBS) can be considered. However, when applying contemporary neurosurgery selection criteria to a naturalistic clinical OCD population, only 1% of OCD patients may meet these criteria.[5] Nevertheless, assuming a cautious 5% of patients with OCD who remain severely impaired and refractory to treatment and a lifetime OCD-prevalence of 0.9% in a population of 13.3 million adults, 5,985 of OCD patients would potentially benefit from neurosurgery.[6–8] GVC for OCD is not routinely performed in the Netherlands and up-to date approximately 100 patients have been treated with DBS for refractory OCD. In other words, there is a severe degree of undertreatment in this vulnerable population, referred to by the WHO as a treatment gap, which is the difference in the proportion of people who have a particular disorder (prevalence) and the proportion of those individuals who actually receive care.[9] The identification of this treatment gap urges the need for an increased awareness of the efficacy, safety, causality and cost-effectiveness of OCD-DBS.

This thesis highlights VC/VS DBS as an effective, well tolerated, and (cognitive) safe treatment option for patients with refractory OCD **(Chapters 2, 5 and 7)**. Nevertheless, the efficacy and safety of OCD-DBS cannot be considered a headline. The Dutch)Healthcare Authority (NZa) established DBS for patients with refractory OCD eligible for reimbursement in

2013.[10] It therefore remains all the more remarkable that according to the 2019 report 'Behoefteraming DBS' instigated by the Dutch Ministry of Health, Welfare and Sport, approximately 10 OCD patients are treated with DBS per year.[11] Factors contributing to this treatment gap are speculative, however, may include a lack of belief in the biology of psychiatric disorders, a social stigma surrounding psychiatry, and ethical concerns surrounding the past experiences with 'psychosurgery'.[12] Considering the latter, in **Chapter 7**, we were unable to find support for previous reports that 'new indications' for DBS, such as OCD, would be more prone to hardware-related AEs when compared to patients suffering from movement disorders, which should reduce referral hesitancy of refractory OCD treating physicians. In line with the view of Mocking *et al.* we acknowledge that increasing awareness among colleagues, students, patients and government officials is pivotal to overcome the social stigma and ethical concerns.[12] We believe that joint efforts of the newly established platform DBS within the Dutch Society for Psychiatry and patient based initiatives such as the Anxiety, Compulsion and Phobia (ADF) or Mind foundations could create synergy to increase the awareness of DBS for OCD and thereby narrowing the treatment gap.

Societal relevance – The economic burden of Deep Brain Stimulation Treatment

The economic consequences of OCD are serious. The cost of illness (CoI) is defined as the value of the resources that are expended or forgone as a result of a health problem. It includes health sector costs (direct costs), the value of decreased or lost productivity by the patient (indirect costs), and the cost of pain and suffering (intangible costs). National CoI estimates for OCD are lacking. In a winder context, the National Institute for Public Health and the Environment (RIVM) reports the direct costs of anxiety disorders to be 773 million Euros, approximately 10% of the total healthcare expenditure on mental and behavioral disorders in 2017.[13] Indirect costs of OCD have been estimated to reflect the direct cost or even be larger.[14,15] Moreover, people with OCD are almost six times as likely to be in problem debt as those without mental problems, possibly due to compulsion related out-of-pocket expenditure.[16]

Cost-effectiveness is a way of expressing costs in relation to effectiveness of two or more alternatives. Effectiveness in cost-effectiveness research is commonly expressed as quality-adjusted life-years (QALYs). The QALY is the product of life expectancy (estimated in years) and its quality over that time.[17] When compared with treatment as usual (TAU), i.e. pharmacological treatment/CBT DBS provides an additional 0.26 QALY.[18] It is estimated that over a 4-year time-span the costs for DBS are €69,287 per QALY and, assuming a willingness to pay a threshold of €80,000/QALY, DBS has 35% probability of being more cost-effective than TAU.[18] In other words, DBS is cost-effective especially considering that productivity changes were calculated according to a human capital approach, which does not consider disability benefits. However,

Following direct operative procedure costs, cost driving factors for DBS treatment include implantable pulse generator changes and management of surgical and hardware related Adverse Events (AEs) requiring additional (partial) removal and replacement. **Chapter 8** provided a cost analysis of treatment options for SSIs following DBS involving a sensitivity analysis to assess the influence of varying the success rate of treatment options. Our results show that initial treatment with antibiotics without immediate hardware explantation results in a reduction of treatment costs of circa 12.1%. However, specifically, aggressive treatment is required in SSIs involving multiple sites or when a S. aureus is identified **(Chapter 7).**

Scientific Relevance – Connectomic Deep Brain Stimulation and collaboration

This thesis draws heavily from developments in the field of neuro-imaging and specifically advances in the context of the connectome i.e. the formal description of parts of the brain and their interconnections.[19] The introduction of the concept of 'the connectome' in 2005 by Olaf Sporns involved parcellating the brain into distinct regions and formally describing a wiring diagram between those regions.[20] Importantly, in this framework two ideas are crucial: First, the degree of parcellation (micro- or macroscale). Second, when describing wiring diagrams mathematically, graph theory is engaged. Considering the former, only a macroscale is truly accessible with Magnetic Resonance Imaging (MRI) research, considering a voxel potentially containing roughly 10^6 neurons. Further advances in DBS imaging methods i.e. preprocessing, electrode localization and estimations of the electric field and volume of tissue activated have allowed to inform us of where a DBS electrode is placed and how specific DBS parameters (e.g., active contacts, amplitude and frequency) will influence the specific portion of tissue or the specific axonal fibers of passage being modulated. The 'marriage' between 'the connectome' and DBS imaging can be regarded to as connectomic DBS and is made readily accessible for researchers by the Lead-DBS toolbox initially developed at Charité – University Medicine (CCM), Berlin.[21] Connectomic DBS have allowed researchers to address specific questions e.g. to which cortical or subcortical areas should DBS electrodes be connected in order to achieve the highest possible clinical improvement.[19] We identified a fiber bundle traversing the anterior limb of the internal capsule (ALIC) connecting the frontal regions to the subthalamic nucleus (STN), functionally recognized as the hyperdirect pathway, to be associated with reduced scores on the Y-BOCS **(Chapter 2)**. Cohort studies and randomized controlled trials of OCD-DBS are typically limited by their low number of included patients, possible due to the previously identified treatment gap, thereby implores scientific collaboration among research groups. Research collaborations can foster greater understanding, knowledge, and may ultimately bring big rewards reward, but may necessitate research groups to aim beyond their personal interests of which **Chapter 3** is a paragon.

Future developments

In 2014, the Neurosurgery Committee for Psychiatric Disorders of the World Society for Stereotactic and Functional Neurosurgery (WSSFN), WSSFN published consensus guidelines for the use of stereotactic neurosurgical interventions to treat refractory psychiatric disorders. The consensus statement noted that, "In this delicate field of neurosurgery for psychiatric disorders, it seems reasonable to state the following requirement before the surgical intervention can be stated as "approved therapy". At least two blinded (if feasible) randomized controlled clinical trials from two different groups of researchers need to be published, both reporting an acceptable risk-benefit ratio, at least comparable with other existing therapies. The clinical trials should be on the same brain area for the same psychiatric indication." The taskforce recognizes two such blinded randomized controlled trials, both using DBS of the ventral anterior capsule region, with only one study considered to be of level 1 evidence According to the Canadian Task Force on the Periodic Health Examination's Levels of Evidence.[22,23] However, the American Society for Stereotactic and Functional Neurosurgery recognizes the study of Mallet et al. (2008) using DBS of the STN as level I evidence.[24] The identification of a unified connectomic target **(Chapter 3)**, rather than regarding the STN and VC/VS as separate targets of stimulation, may prompt the World Society for Stereotactic and Functional Neurosurgery (WSSFN), to reconsider their statement regarding DBS remaining an emerging, but not yet established therapy for OCD.[25] The acknowledgement of OCD-DBS as an established treatment modality would significantly contribute to relieve the social stigma and cast away the shadows of the 'psychosurgical' past and thereby aid to close the treatment gap. However, and here we echo the view of the WSSFN, this treatment should be reserved for those individuals with demonstrated treatment-refractoriness and should only be carried out at dedicated, experienced units with strong affiliations with multidisciplinary research teams.

Nevertheless, After DBS, patients often still need medication, and CBT is often offered because it is considered useful in the treatment of remaining obsessive and compulsive symptoms, in dealing with behavior that has become habitual and persists even when the urge has subsided, and in helping to adjust to the new situation and expectancies. In addition, CBT provides the patient with new coping styles and problem solving skills that may be important to prevent relapse and contribute to the long-term efficacy of DBS. Whereas guidelines for CBT in OCD have suggested offering CBT after DBS, clinical practice varies widely across institutions and often depends on local possibilities and traditions.[26] As discussed in **chapter 6**, the current literature trials explicitly focusing on the effectiveness of CBT added to DBS is scarce. Since the overall treatment effect is the combined result of DBS, medication and CBT, future trials should be designed in such a way that they allow quantification of the effect of add-on therapies in OCD patients treated with DBS. Only this way can information be gathered that would contribute to the development of an algorithm and clinical guidelines for concomitant therapies to optimize treatment effects in OCD patients being treated with DBS.

Although the aforementioned preliminary study identifies DBS as cost-effective compared to treatment as usual, we anticipate that closing the treatment gap of therapy refractory OCD may impose a significant economic burden. Future studies should establish the cost-effectiveness of OCD including more patients, costs due to social benefits and a long term follow-up. Ultimately, further studies into underlying mechanisms will pave the way for non-invasive lesioning surgery such as GVC which would probably be as effective and certainly less costly.

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