

Neurosurgery in Obsessive Compulsive Disorder

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Summary

The basis for contemporary psychological models of obsessive compulsive disorder (OCD) is the well-established assertion that unwanted, intrusive thoughts, images and impulses occur in most people in the general population. Most people are able to deal well with these thoughts, images and impulses, using adequate coping strategies. However, according to the cognitive behavioral theories, in some people these intrusive cognitions may develop into clinical obsessions. OCD prone individuals through several cognitive processes. First, an intrusive thought is appraised as being the individual's personal responsibility, or is threatening. Secondly, as these intrusive cognitions will cause significant distress, and when more common distraction strategies fail, the affected individual will develop a neutralizing response, either overt, through compulsive behavior, or covert, through thought rituals, which aim to directly reduce the anxiety arousing effects of the obsession. The engagement of these neutralizing activities may lead to an increase in the salience of the obsession, which therefore lead to an increase of the intrusive thoughts and thus to an increase of neutralizing activities again, thereby entering a vicious cycle. It may be clear that for the complex of psychiatric symptoms encountered in OCD no single cortico-basal ganglia-thalamocortical loop can be identified. Rather, multiple anatomical parallel fronto-striatal circuits may be identified.

A range of interventions is effective in the management of OCD including behavioral therapy, cognitive therapy and cognitive behavioral therapy (CBT). In addition, a large body of evidence advocate on the use of selective serotonin reuptake inhibitors (SSRIs) and clomipramine, a tricyclic antidepressant, in the treatment of OCD, often used in combination with CBT. However, 40-60% of patients remain treatment-refractory, defined as a less than 25% reduction in Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score. This may urge the need for alternative treatment strategies, such as deep brain stimulation (DBS) of subcortical structures or gamma knife ventral capsulotomy (GVC).

The first part of this thesis aimed at identifying fiber bundles associated with clinical response to DBS or GVC. OCD patients consistently underperform across multiple cognitive domains. The second part of this thesis was focused on the neuropsychological outcome of OCD DBS in order to identify a cognitive pattern associated with a good outcome or that would (in part) help explain the functional mechanism of OCD-DBS. The third part focused on several postoperative aspects of (OCD)-DBS patients including surgical and hardware related adverse events of DBS and reviewing the effectiveness, timing and procedural aspects of CBT after DBS with the aim to provide clinical recommendations.

Part I - Anatomical considerations

Chapter 2 provides a detailed clinical description and treatment outcome analysis in a cohort of 8 refractory OCD patients receiving ventral capsule/ ventral striatum (VC/VS) stimulation. Primary outcome measures the Y-BOCS) and secondary outcome measures (depressive symptoms, quality of life and global health) were retrospectively analyzed. DBS leads were warped into standard stereotactic space and a normative connectome was used to identify the neural network associated with clinical outcome. With a median stimulation duration of 26 months, patients exhibited a mean Y-BOCS reduction of 10.5 resulting in a response rate of 63%. Modulation of 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, was associated with Y-BOCS reduction. Our findings show that in VC/VS stimulation, the same neural network is associated with beneficial clinical outcome when compared to other targets i.e. (ALIC), the nucleus accumbens or the STN, which supports the evolvement from the concept of an optimal gray matter target to conceiving the target as modulating a symptomatic network.

Chapter 3 provides a critical review in which we aim to integrate findings from connectomic studies and deep brain stimulation interventions to characterize a neural network presumably effective in reducing obsessions and compulsions. Recent advancements, as illustrated in **Chapter 2**, suggested that changes in broader networks, instead of the local impact at the stimulation site alone, are responsible for improvement of obsessions and compulsions. These findings were fueled by innovative methodological approaches using brain connectivity analysis in combination with neuromodulative interventions. Such a connectomic approach for neuromodulation constitutes an integrative account that aims to characterize optimal target networks. To this end, we scrutinize methodologies and seemingly conflicting findings with the aim to merge observations to identify common and diverse pathways for treating obsessive-compulsive disorder. Ultimately, we propose a unified network that – when modulated by means of cortical or subcortical interventions – alleviates obsessive-compulsive symptoms.

In **Chapter 4**, we analyzed pre- and postoperative images of 8 patients who underwent GVC were used to correlate lesion characteristics with symptom improvement. Normative diffusion MRI based tractography was used to determine networks associated with successful lesions. This study highlighted the efficacy of GVC in patients with treatment-refractory OCD. We were not able to identify discriminative fiber tracts associated with clinical response, nor to predict clinical outcome using previous identified tracts in DBS, implicating interpatient variability i.e. fiber organization in the anterior limb of the internal capsula explanatory for treatment variability. The strongest correlation with symptom improvement was found for a decrease of the left ventral diencephalon volume ($r=-0.83$, $p=0.039$). These results support previous findings that both ablative and non-ablative

treatment strategies for treatment-refractory OCD restore frontostriatal network activity. Future research should focus on elucidating neuroanatomical substrates of OCD symptom dimensions and ideally identify the optimal for structural profile relevant to treatment targets.

Part 2 – Neuropsychological considerations

Chapter 5 assessed the cognitive safety and explored explanatory treatment mechanisms of DBS for OCD through a systematic review combined with a case-series. EMBASE, PubMed/Medline, Psycinfo and the Cochrane Library were systematically searched for studies reporting neuropsychological outcomes following DBS for OCD. Searches were completed to November 2020. Included studies were appraised for study design and quality according to NIH quality assessment tools. For the case series, the neuropsychological outcomes of seven patients were retrospectively assessed. Changes from baseline and last follow up were analyzed and compared to clinical improvement. Five randomized controlled trials and nine observational studies comprising a total 171 patients were analyzed collectively. Variable outcomes were observed in the domains of attention and memory, executive functioning and in particular cognitive flexibility. In the case series, the Trail Making Test ratio, which is indicative for cognitive flexibility, showed a significant decrease, with a medium effect size of 0.63. Although individual studies generally do not report cognitive deterioration after DBS for OCD, the variability of study designs and the multitude of cognitive measures precluded a meta-analysis to confirm its safety and recognition of a cognitive pattern through which the efficacy of DBS for OCD might be explained. Future, prospective studies should include a standardized neuropsychological assessment specifically addressing executive functioning and longer-term follow-up in order to demonstrate the cognitive safety of the procedure, and contribute to our understanding of the working mechanism of DBS in OCD.

Chapter 6 provides a systematic review with the aim to assess the efficacy, timing and procedural aspects of postoperative CBT in OCD patients treated with DBS. After initiating DBS many patients still require medication and/or behavioral therapy to deal with persisting symptoms and habitual behaviors. The clinical practice of administering postoperative cognitive behavioral therapy (CBT) varies widely, and there are no clinical guidelines for this add-on therapy. In this systematic we included 5 original studies, one case series and three reviews. Only two clinical trials have explicitly focused on the effectiveness of CBT added to DBS in patients with therapy-resistant OCD. These two studies both showed effectiveness of CBT. However, they had a distinctly different design, very small sample sizes and different ways of administering the therapy. Therefore, no firm conclusions can be drawn or recommendations made for administering CBT after DBS for therapy-resistant OCD. The effectiveness, timing and procedural aspects of CBT added to DBS in therapy-resistant

OCD has hardly been studied. Preliminary evidence indicates that CBT has an added effect in OCD patients being treated with DBS. 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.

Part 3 – Surgical aspects

Introducing DBS in OCD imposes new challenges such as committing patients to a lifelong implant at a younger age. In **Chapter 7**, we assessed patients undergoing DBS related procedures between January 2011 and July 2020 and retrospectively inventorised adverse events (AEs). In this period 508 DBS related procedures were performed including 201 implantations of brain electrodes in 200 patients and 307 implantable pulse generators (IPG) replacements in 142 patients. The mean follow-up time was 43 ± 31 months. Univariate logistic regression analysis was used to assess the predictive value of selected demographic and clinical variables. Surgical or hardware related AEs following initial implantation affected 40 of 200 patients (20%) and resolved without permanent sequelae in all instances. The most frequent AEs were surgical site infections (SSIs) (20/201, 9.95%) and wire tethering (2.49%, 5/201) followed by hardware failure (1.99%, 4/201), skin erosion (2/201, 1.0%), pain (1/201, 0.5%) lead migration (2/386, 0.52% electrode sites) and hematoma (2/386, 0.52% electrode sites). The overall rate of AEs for IPG replacement was 5.6% (17/305). No surgical i.e. staged or non-staged, electrode fixation or patient related risk factors were identified for SSI or wire tethering. Major AEs involving intracranial surgery related AEs or AEs requiring surgical removal or revision of hardware are rare. In particular, this analyses did not support previous reports of new indications such as OCD, epilepsy and TS being more prone to undergo hardware-related AEs when compared to PD patients. Specifically, aggressive treatment is required in SSIs involving multiple sites or when a *S. aureus* is identified. For future benchmarking, the development of a uniform reporting system for surgical and hardware related AEs in DBS surgery would be useful.

Chapter 8 provided a cost analyses of treatment options of one of the most distressing hardware-related complication of DBS, infection. These infections can be either treated with antibiotics or with removal of the infected hardware followed by reimplantation. In our experience the success of antibiotic therapy was about 50%. Here, we have investigated the costs of treating the infection with antibiotics only with the risk of surgery when unsuccessful versus immediate removal followed by reimplantation. We calculated the costs of the different strategies through a standard costing procedure. A decision model has been applied to establish the average treatment cost per patient representative for a clinical setting

where both strategies are employed. Subsequently, a sensitivity analysis has been performed to assess the influence of clinical assumptions regarding the effectiveness of antibiotics treatment on average treatment costs. The costs of treating a case of DBS hardware infection with immediate IPG replacement surgery were €29,301 and €9499 for successful antibiotic treatment. For antibiotic treatment followed by IPG replacement surgery the total costs were €38,741. Antibiotic treatment alone was successful in 44% (4/9) of the included cases of DBS infection, resulting in an average treatment costs per patient of €25,745. Trying to resolve DBS hardware infections initially with antibiotics reduced treatment costs by 12.1%. Treatment with antibiotics with the risk of a later removal when unsuccessful was a more valuable strategy in terms of costs when compared to immediate surgical intervention in cases of hardware-related infections in DBS surgeries.

The general discussion in **chapter 9** is divided into two parts. In the first of part, common themes within and between the parts of this thesis will be discussed more thoroughly in light of identifying neurosurgery as an accepted therapy for refractory OCD. In the second part, a neuro-computational model of OCD will be introduced including a delineation of its anatomical constituents, as identified in this thesis, within the cortico-basal ganglia- thalamo-cortical feedback loop environment.