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Neurosurgery in Obsessive Compulsive Disorder

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Neurosurgery in Obsessive Compulsive Disorder

Tim A.M. Bouwens

Neurosurgery for Obsessive Compulsive Disorder

From targets and treatment to tracts and back again

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Neurosurgery in Obsessive Compulsive Disorder

From targets to treatment to tracts and back again

PROEFSCHRIFT

Ter verkijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. Pamela Habibovic
volgens het besluit van het College van Decanen, in het openbaar te verdedigen
op 6 oktober 2022, om 16:00 uur.

Door

Tim Antonius Martinus Bouwens

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dr. K. Rijkers

Voor Madelon, Julia, Roos en Nova

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Chapter 1

Introduction

Historical perspective of neurosurgery for psychiatric disorders

The origins of psychosurgery can be traced back to antiquity, with evidence of Stone Age craniotomies dating as far back as 5100 BCE.[1] Archaeological findings suggest that prehistoric shamans could access the brain through trephination, a process that involves the drilling or incision of a hole in the skull using a bladed surgical tool.[2] Motives inferred for the execution of trephinations remain speculative, but we can assert it was performed for head injuries, brain disorders or mental diseases. Trephination has been well documented throughout early history leading into premodern times, as illustrated by the famous painting *The Extraction of the Stone of Madness* (circa 1494) by Hieronymus Bosch, figure 1.

Figure 1. The Extraction of The Stone of Madness (or The Cure of Folly) by Hieronymus Bosch. Museo del Prado, Madrid, Spain

Clearly, there has been a longstanding interest in the brain–behavior relationship converging in the mid-19th century following the case of Phineas Gage, a 25-year railroad worker who was speared by a rod measuring 109 cm long and 3 cm thick through his prefrontal cortex during an unfortunate workplace explosion.[3] Gage survived, but the mental and behavioral changes were profound. Gage changed dramatically to an obstinate irreverent and socially uninhibited individual, later recognized as the frontal lobe syndrome.[3] It was perhaps the first case to suggest the role of brain areas in determining personality and which specific parts of the brain, when affected, can induce specific mental changes. In this light, his case contributed to the emergence of the scientific approaches that fostered the emergence of psychosurgery in the 20th century.

Upon presentation of a momentous experiment in which two chimpanzees had bilateral resections of the prefrontal cortex by Dr. John F. Fulton (1899-1960) in a plenary session for psychosurgery during the Second International Neurologic Congress held in London in 1935, Dr. Antonio Egas Moniz (1874-1955), Professor of Neurology at the University of Lisbon, and his collaborator, the neurosurgeon Dr. Almeida Lima (1903-1985) began pioneering with frontal leucotomy. Specifically, bifrontal white matter connections between frontal cortices and the thalamus were severed to alleviate severe mental illness including depression and schizophrenia in long-term hospitalized patients.[2] In 1949 Dr. Moniz had received the Nobel Prize for his pioneering work on frontal leucotomy. Across the pond, frontal (transorbital) 'icepick' lobotomy was introduced by dr. Walter Freeman (1895-1972). The rationale for frontal lobotomy, as for frontal leucotomy, was to try to

improve psychiatric symptoms by reducing emotional reactivity. By the end of the 1940s lobotomy was used as a treatment for schizophrenia, depression and 'obsessions and compulsions and other neurosis' and was performed in more than half of American psychiatric hospitals.[2] However, severe side effects, such as apathy, psychomotor slowing, amnestic disorders, and faecal and urinary incontinence, were not uncommon following lobotomy.[4] Moreover, the procedure was associated with a mortality rate of up to 6%,

It must be remembered that the movement toward psychosurgery did not occur in a vacuum. First, at the time, pharmacological treatment was not available and psychotherapy was often not effective or unavailable. Considering the life debilitating aspect of mental illnesses, treating physicians felt compelled to come up with effective treatments to ameliorate symptoms. Moreover, as no alternative treatment strategies were available, hospitalization and physical containment measures were often the only treatment measures available, imposing a significant socioeconomic burden on society.

Nevertheless, after observing a frontal leucotomy and consequent severe side effects, Ernest A. Spiegel (1895–1985) and Henry T. Wycis (1911–1971) were prompted to develop a stereotactic apparatus to perform lesioning of the medial nucleus of the thalamus (medial thalamotomy) in order to minimize injury to the cerebral cortex and white matter.[5] The first stereotactic operations for 'obsessive-compulsive neurosis' were presented in a preliminary *Science* report in 1947.[6] *It is here that we recognize neurosurgery for psychiatric disorders diverging away from historical psychosurgery.* Soon after Spiegel and Wycis demonstrated the first stereotactic procedure in humans, Lars Leksell (1907-1986) began developing a method for delivering radiation to the brain stereotactically. Rather than placing a probe inside the brain and creating a thermal lesion, he used focused ionizing radiation (X-rays) to produce the same effect without open surgery. In 1953, 4 years after the first description of RF capsulotomy, Leksell performed the first radiosurgical capsulotomy.[7] Deep Brain Stimulation (DBS) represents an evolution of the stereotactic procedures as first demonstrated by Spiegel and Wycis.

Since ancient times, electrical stimulation has been used in attempt to modulate the nervous system and to treat some neurological disorders. Scribonius Largo, physician of the Roman emperor Claudius, in his text "Compositiones medicamentorum" (46 AD) suggested the application of electric ray (*Torpedo torpedo* and *Torpedo nobiliana*) on the cranial surface as a remedy for the headache. These fishes are known for being capable of producing an electric discharge and were later used for the treatment of seizures, depresSsion, and pain until the eighteenth century.[8] Spiegel and Wycis systematically used intra-operative electrical stimulation of subcortical structures for confirming the target for ablation. These observations led to suggest that these stimulations of deep cerebral nuclei could be used not only as a method for diagnostic purposes but also as a therapeutic method itself. Early pioneers in brain-stimulation aimed at treating mental disorders were José M. Delgado (Yale University, Connecticut) and Robert Heath (Tulane University, New Orleans). Delgado (1915-2011) implanted electrodes that established two-way communications with the brain in mobile animals which allowed stimulating different regions, producing changes in affect

and behavior. Encouraged by these results, Delgado extended his research to patients with chronic refractory epilepsy and schizophrenia. As early as the 1950s, Heath also implanted electrodes in studies involving people with schizophrenia, violent behaviour and depression. Nevertheless, the effects of electrical stimulation were imprecise, poorly replicated and yielded no useful therapeutic outcomes. This egregious research was conducted in a staggering ethical vacuum including the lack of informed consent, poor documentation and poor interpretation of empirical research considering the anatomical targets which were used for stimulation. Simultaneously, neuropsychopharmacology thrived. The development of drugs for most types of psychiatric disorder prompted deinstitutionalization. This, together with the raised ethical concerns and a changing scientific, political, and social Zeitgeist occurred, left the field of electrical simulation for psychiatric disorders in controversy. Several decades later, driven by the observation of concomitant improvement in mood and OCD symptomatology in patients treated with DBS for Parkinson's disease and the identification a considerable amount of OCD patients were therapy resistant, renewed interest in DBS arose.

Obsessive compulsive Disorder: clinical aspects summarized

In the fifth edition of the Diagnostic and Statistics Manual (DSM 5) Obsessive compulsive disorder (OCD) is characterized by the presence of obsessions, defined as 'recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress', and/or compulsions, defined as 'repetitive behaviors or mental acts that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly'.[9] OCD is heterogeneous condition with patients presenting with a constellation of obsessional concerns and compulsive behaviors, which prompted the identification of four symptom clusters including contamination obsessions and compulsions, repugnant obsessions with mental and checking compulsions, obsessions about responsibility for causing disasters and checking or reassurance-seeking compulsions and symmetry obsessions and compulsions.[10] The variation in clinical symptomatology is further amplified by the evolution of symptoms of an individual over time, as symptoms naturally wax and wane, and might differ topographically i.e. aggressive obsessions are more common in Brazil, while religious obsessions are more common in the Middle East, and contamination is more common in Western-countries.[11] Some aspects of OCD, however, are homogenous across cultures including a higher prevalence in women, onset at an early age and relatively frequent resistant to psychotherapy and pharmaco-therapy.

The diagnosis of OCD is usually established through the use clinical interviews; as screening instruments are relatively time consuming in daily practice. In contrary, many assessments instruments have been developed to capture the core symptoms and severity

of OCD. The current golden standard to asses OCD severity is the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS).[12] Five main aspects: frequency or time spent, degree of interference, distress, resistance and perceived control, of both obsessions and compulsions are scored on a 0 (no symptoms) to 4 (extreme symptoms) scale summed to yield a maximum of 40 points.[12] Severe to extremely severe OCD is thresholded at a Y-BOCS score of 35-40, moderate to severe symptoms correspond with scores of 26–34, moderate symptoms rate at scores of 14–25 and scores of 0-13 correspond with mild or subclinical symptoms of OCD.[13]

The lifetime prevalence of OCD is estimated between 1% and 3%, with prevalence rates up to 2.3% for individuals between 30 and 40 years, and up to 0.7% of adults aged 60 years or older.[14] OCD often debutes in childhood, between the ages of eight and eleven, with an increase in prevalence during puberty and again in early adulthood.[14,15] It is possible for OCD to occur later in life, with an estimated prevalence of 8.6% of all cases with an onset over the age of 40.[16] Twin studies have estimated that half of the individual variation in OCD symptoms is due to environmental risk factors with shared as well as unique factors for childhood and adult OCD. Environmental risk factors for adulthood OCD are pregnancy, traumatic life events and substance abuse.[17] Familial studies of OCD subjects show a familial aggregation of OCD. The glutamate transporter gene SLC1A1 is the only gene that has been consistently identified across OCD samples.[18]

OCD is not a discrete disorder: an estimated 60-90% of OCD individuals have psychiatric comorbidity.[19] Among these mood disorders, i.e. major depressive disorder, and anxiety disorders are the most prevalent.[19,20] OCD is associated with higher risk of suicide and an increased risk of metabolic and cardiovascular disorders[21,22] A broad spectrum of Quality of Life domains are markedly affected in individuals with OCD, including the ability to work and perform household duties, subjective sense of wellbeing, social relationships, and ability to enjoy leisure activities compared with community norms.[23] QoL is associated with OCD severity, particularly obsessional severity and comorbid depression severity. Exploratory results recognize a score of 20 on the Yale-Brown Obsessive-Compulsive Scale (0-40) to be a pivotal point from which QoL and psychosocial functioning begins to be more significantly affected.Further illustrated by observations that people with chronic OCD spend an average of 6 hours occupied by obsessions and 4.5 hours per day engaging in compulsions, the World Health Organization lists anxiety disorders, including OCD, as the sixth largest contributor to non-fatal health loss globally.[24]

Prior to the first pharmacotherapeutic studies in the 1980's, the diagnosis of OCD offered little to no hope for the affected individual. In the following decades, a number of agents have been found effective in the treatment of OCD including, selective serotonin reuptake inhibitors (SSRIs) and clomipramine. Cognitive-Behavioral Therapy, however, should be provided initially or prior to, or concurrent with, first-line pharmacotherapy, when available[25]. Figure 2 contains a contemporary treatment algorithm of OCD, adapted from Borue *et al.*[25] A patient can be considered treatment refractory, if he/she fails to respond to CBT, two trials with an SSRI, clomipramine augmentation and additional therapy with

antipsychotics. Failure to respond is commonly defined as a less than 25% reduction on the Yale-Brown Obsessive-Compulsive Scale Y-BOCS.[26] It is estimated that approximately 40-60% of the patients are treatment refractory. For these patients several alternative treatment strategies may be effictive, e.g. ablative surgery or deep brain stimulation.

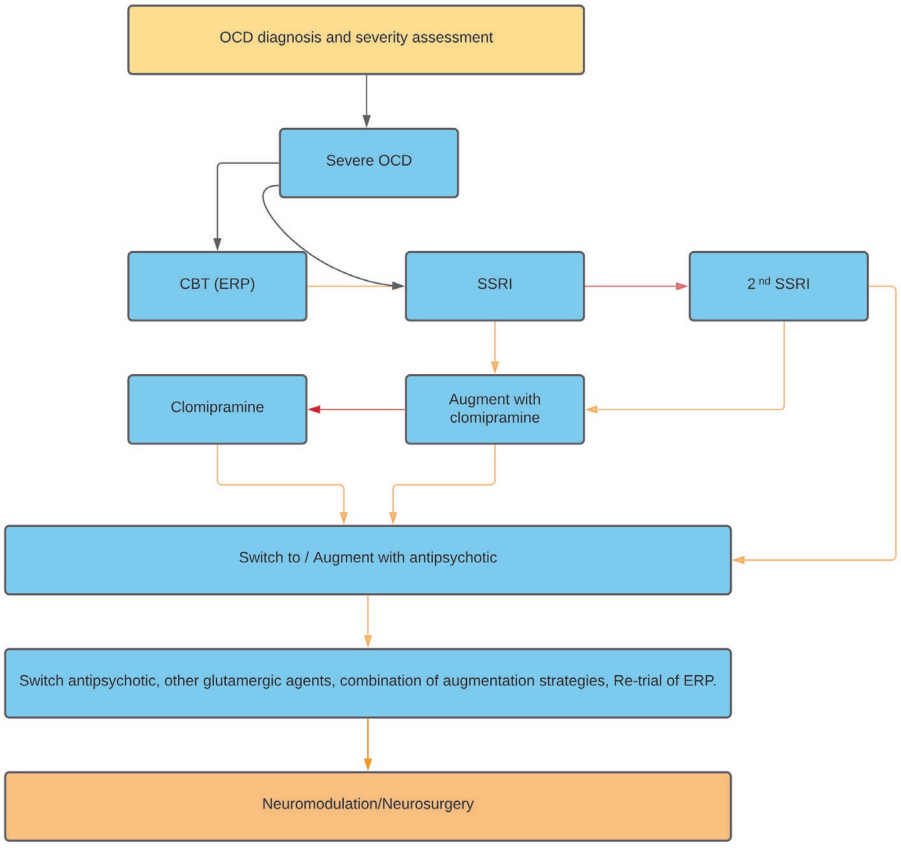

Figure 2. Treatment algorithm for OCD. ERP is recommended for individuals suffering from severe OCD and concurrently with an SSRI i.e. fluvoxamine or sertraline for severe cases of OCD. For individuals with a partial response to CBT and an initial or second trials of SSRI therapy could be augmented with clomipramine, with clomipramine monotherapy might be beneficial after failing of SSRI augmented with clomipramine. Orange arrows: no or partial response; Red arrows: no response. OCD: Obsessive compulsive disorder; SSRI: serotonin selective reuptake inhibitors; CBT: cognitive-behavioral therapy; ERP: Exposure Response Prevention.

Contemporary neurosurgical approaches for the treatment of Obsessive Compulsive Disorder

Four main ablative procedures have emerged for treatment-refractory OCD: anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy and limbic leucotomy (a combination of ventral cingulotomy and subcaudate tractotomy).[27,28] Contemporary techniques for ventral capsulotomy include Gamma Knife radiosurgery, magnetic resonance-guided ultrasonography (MRgFUS, or Focussed Ultrasound) and laser interstitial thermal therapy (LITT).[27,29,30] Here, within the scope of this thesis, we will briefly discuss only ventral capsulotomy using Gamma Knife radiosurgery (GVC).
Moving forward from the first radiosurgical capsulotomy, between 1976 and 1979, Leksell treated patients with anxiety disorders, of whom several suffered from OCD, with the first prototype of the Gamma Knife. Another cohort was treated in with the second Gamma Knife prototype (GK II) at the Karolinska Institute in 1985, with treatment plans aiming to cover the same anatomical region as in the first cohort.[31] Clinical benefit was observed for 36 to 56% of the patients. Building upon these early observations, several GVC programs emerged globally.[7,32,33] Although treatment plans varied across programs with different anatomical locations of the target in dorsal-ventral extension within the ALIC, various amounts of isocenters, different dosage used and technical aspects, these studies indicated that bilateral GVC for refractory OCD might be an effective treatment modality. Up to date, there is one double-blind, sham-controlled randomized trial using GVC for OCD. In this trial Lopes *et al.* (2014) randomized 16 patients with intractable OCD to active (n = 8) or sham (n = 8) GVC. At the end of the blinding phase of 12 months, two participants of the active treatment arm responded, whereas none of the 8 sham-GVC group patients responded (response was defined here as a reduction of 35% or more of the Y-BOCS) After unblinding, patients assigned to the sham condition were offered active GVC. After a follow-up of 54 months, 3 additional patients in this group had become responders. Of the 4 sham-GVC patients who later received active GVC, 2 responded by post-GVC month 12.[34] The largest prospective cohort study was published in 2017 which included a total of 55 treatment refractory OCD patients receiving GVC.[35] Initially, 14 patients received a bilateral single-shot centrally in the internal capsule one-third of the distance dorsally from the capsule's most ventral extension. After a mean follow-up of 9 months, no significant differences in mean Y-BOCS scores were observed, whereafter patients received an additional bilateral shot immediately ventral to the first stage shot in the center of the capsule. In these 40 patients receiving a bilateral double shot, substantial improvement in Y-BOCS scores were observed with reported response rates of 59% after 12 months of follow-up increasing to 69% after two-years.[35] Observed side effects included significant brain edema requiring steroid treatment (9%) with headache (without additional symptoms), asymptomatic lacunar infarcts of the caudate nucleus (11%) and asymptomatic brain cysts (5%). Of note, one patient developed extensive bilateral edema with radionecrosis and cyst formation despite attempts to drain the cyst, a course of bevacizumab, and placement of a shunt, ultimately requiring open resection of the necrotic material.

DBS treatment for OCD

Based on the observed efficacy of anterior capsulotomy, Nuttin *et al,* showed the clinical efficacy of electrical stimulation of the anterior limbs of the internal capsules (ALIC) in three patients in 1999.[36] In the following years, several small sized controlled and open-label studies applied DBS at several locations along the rostral–caudal extent of the anterior limb of the internal capsule, thereby developing the target site as the junction of the ventral capsule/ventral striatum (VC/VS).[37] Clinical efficacy ofVC/VS stimulation was confirmed by the publication of two randomized sham-controlled/counterbalanced trials, with a mean Y-BOCS reduction of 43%. Moreover, in the open phase of a sham-controlled RCT including 16 OCD patients undergoing DBS of the nucleus accumbens (NAc), no clinical changes were observed after the active contacts were switched to the more dorsal contact points, thereby stimulating the ventral ALIC, rather than the gray matter of the NAc.[38] These studies collectively observed a drastic concomitant improvement of comorbid depressive symptoms and anxiety. In parallel, the interest of the subthalamic nucleus (STN) as a target for DBS in OCD was fueled by case observations of patients with advanced Parkinson's Disease and comorbid OCD treated with STN-DBS, resulting in an improvement of the Parkinsonian symptoms and a substantial reduction of obsessive and compulsive symptoms.[39,40] Based on these findings, a larger double-blind cross-over study of STN-DBS was performed including 17 patients, showing a response rate of 70% defined as a reduction of 35% or more of the Y-BOCS and 62% of patients achieved satisfactory global functioning.[41] In addition to the STN andVC/VS several other targets for stimulation are defined including the superolateral branch of the medial forebrain bundle (slMFB), medial dorsal and ventral anterior nuclei of the thalamus (MD/vANT), the inferior thalamic peduncle (ITP), the bed nucleus of the stria terminalis (BNST) and the anterior cingulate cortex (ACC), predominantly investigated in case series or reports.[42]

The reported incidence of surgical and hardware related adverse events (AEs) following OCD-DBS are low. In the meta-analyses of Alonso *et al.* DBS related adverse events such as intracerebral hemorrhage occurred in 3% of the included patients (n=161). The most prevalent hardware adverse events were found to the feeling of extension leads, mainly in the area of neck and ear (10%) and hardware disconnection (3%). The most frequent stimulation-related adverse effect was a hypomanic state or some kind of mood disinhibition, reported in nearly one from five patients. Transient worsening of anxiety while searching for optimal stimulation parameters was also been frequently described. Nevertheless, almost all studies described these stimulation-related adverse effects as mild, transient and reversible after the adjustment of the stimulation parameters.[42]

The World Society for Stereotactic and Functional Neurosurgery (WSSFN) consensus guideline positions ventral capsule/ventral striatum (VC/VS) DBS as an emerging, but not yet, established therapy for severe treatment resistant OCD.[43,44] In parallel, the American Society For Stereotactic and Functional Neurosurgery Association of Neurological Surgeons (ASSFN)/Congress of Neurological Surgeons (CNS), reserves STN–DBS for medically refractory OCD. Both recommendations are based on two different, level I/II

Randomized Controlled Trials (RCTs), according to the Canadian Task Force on the Periodic Health Examination's Levels of Evidence, targeting either the VC/VS or the STN.[41,45,46] The apparent disagreement of the target of stimulation is generated by incongruous interpretation of levels of evidence, consensual guidelines or preference, but ultimately resembles the challenges faced by clinical studies reporting the outcome for OCD-DBS.

General introduction into Cortico-Basal ganglia-Thalamocortical feedback loops (CBGTs)

The anatomical basis for Cortico-Basal ganglia-Thalamocortical feedback loops (CBGTs) was provided in the mid-1980s. Alexander *et al*. originally proposed five parallel but functionally segregated pathways, originally named after the involved corresponding cortex.[47] Advances in brain-imaging techniques have now identified a set of seven reliably reproducible major networks, subdivisible into a finer set of 17 smaller subnetworks.[48] CBGTs involve connections between the cortex, the basal ganglia, the thalamus and back to the cortex. Figure 3 contains a coronal MRI section at the level of the dorsolateral prefrontal cortex with the CBGT involved subcortical structures.

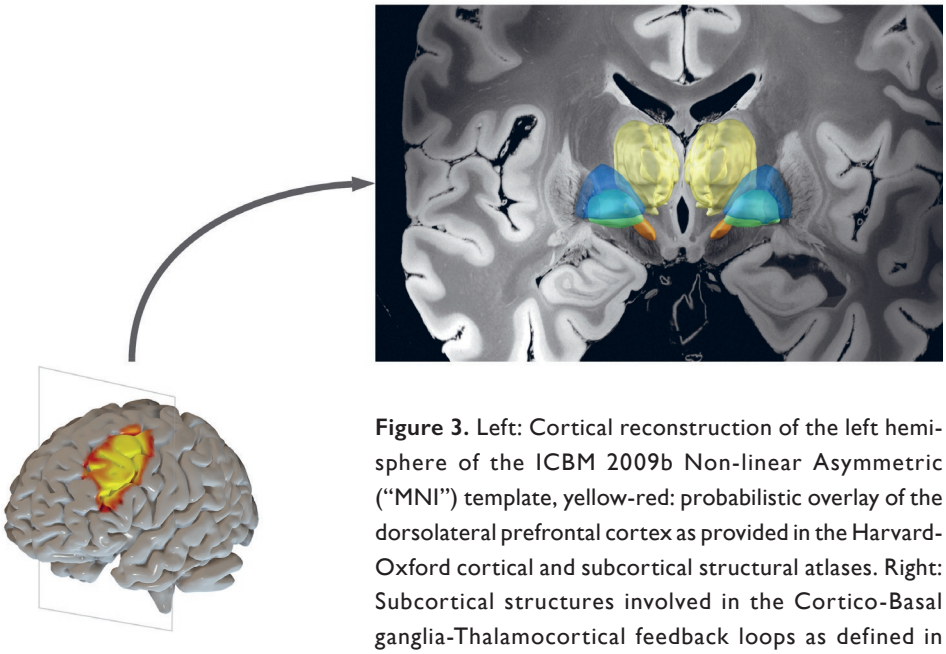

Figure 3. Left: Cortical reconstruction of the left hemisphere of the ICBM 2009b Non-linear Asymmetric ("MNI") template, yellow-red: probabilistic overlay of the dorsolateral prefrontal cortex as provided in the Harvard-Oxford cortical and subcortical structural atlases. Right: Subcortical structures involved in the Cortico-Basal ganglia-Thalamocortical feedback loops as defined in DISTAL Atlas visualized in the 7 Tesla MRI of the ex vivo human brain at 100 micron resolution registered in MNI space. Yellow: Thalamus; Blue: Globus pallidus externa; Green: Globus pallidus interna; Orange: Subthalamic nucleus.

Two major pathways between the striatum and internal globus pallidus (GPi)/ substantia nigra *pars reticulata* (SNr) have been identified: (1) a direct, monosynaptic connection to both output nuclei (GPi and SNr) and (2) an indirect, polysynaptic pathway that first targets the external globus pallidus (GPe), and involves additional projections from GPe to the output nuclei, both directly, and via a loop through the subthalamic nucleus (STN).[49] Another non-striatal CBGT has been described, the so-called hyperdirect pathway that involves direct cortical projections from the cortex to the STN. Figure 4 contains a schematic wiring scheme of the CBGT pathways.

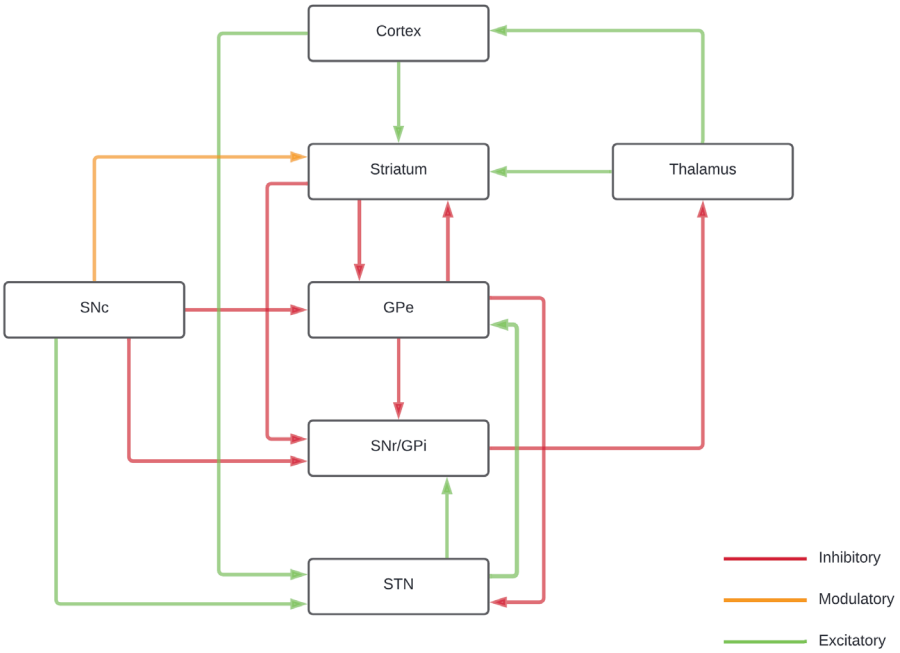

Figure 4. Schematic wiring scheme CBGT pathways (associative circuit) Afferents to the striatum originate from the cerebral cortex (glutamatergic), thalamus (glutamatergic), and the brain stem. The ventral striatum includes striatal elements of the olfactory tubercle, ventral and medial parts of the caudate–putamen complex, as well as caudal areas of the caudate–putamen located dorsal to the amygdala. Efferent (i.a. GABAergic) fibers from the striatum project topographical to the pallidal complex, comprising of the ventral pallidum (VP), globus pallidus externus (GPe) and internus (GPi) and the substantia nigra (both pars compacta (SNc) and pars reticulata SNr). Projections (GABergic) from the GPi and the SNr terminate in the VA and CM nucleus of the thalamus of which fibers arise (glutamatergic) that close the loop to form the direct pathway. The STN receives input from parts of the VP and the GPe, importantly the GPe and STN connection is considered to be reciprocal. The STN in turn, projects to the GPi, forming the indirect pathway respectively. The STN directly receives input from the cortex, referred to as the hyperdirect pathway.

A growing body of evidence conflicts with the traditional view that these pathways act as independent levers for facilitating (i.e., direct pathway) or suppressing (i.e., indirect pathway, hyperdirect pathway) motor output, suggesting instead that they engage in a dynamic competition during action decisions that computationally captures action uncertainty, figure 5.[50]

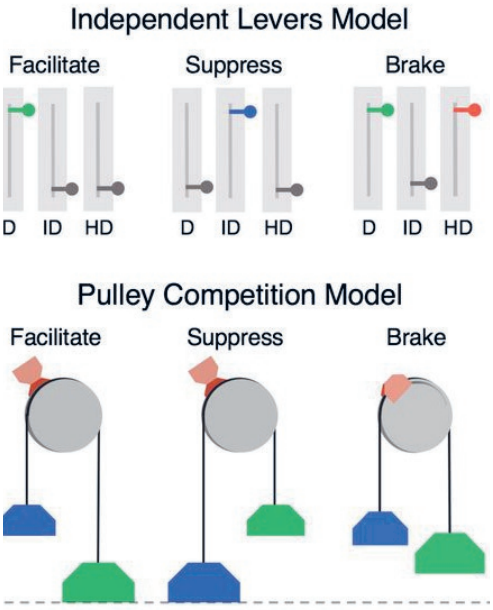

Figure 5. Independent Levers Model assumes that the direct (left, green), indirect (middle, blue), and hyper-direct (right, red) pathways are structurally and functionally segregated. D: Direct pathway; HD: indirect pathway; ID: indirect pathway. Each pathway works individually in facilitating, suppressing, or braking output of the Basal ganglia. In contrast (below), the Pulley Model assumes that the direct and indirect pathways compete throughout the BG, with the strength of each pathway acting as weights on opposing sides of a pulley. As activation in the direct pathway overpowers that of the indirect pathway, this imbalance accelerates the network toward 'facilitation, resulting in an executed action when the difference reaches a critical threshold (dotted line). In the event of a stop cue, the action can be reactively cancelled if the pulley brake (red brake pad) is activated before the direct-indirect difference reaches a critical threshold. The accelerating (e.g., nonlinear) dynamics of an imbalanced pulley lead to less efficacious braking when the network is pulled further toward action execution (e.g., longer brake streaks on pulley wheel). This dependency illustrates how proactive modulation of the direct-indirect balance may influence reactive stopping via activation of the hyper-direct pathway. Figure by Dunovan 2016 distributed under the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0).

Neuroanatomy of the Anterior Limb of the Internal Capsule.

The Anterior Limb of the Internal Capsule (ALIC) carries both ascending and descending fibers connecting the prefrontal cortical areas that are associated with different aspects of emotion, motivation, cognition processing and decision making with areas such as the STN and ventral thalamus.[51] These cortical areas include the dorsomedial prefrontal cortex (dmPFC), the dorsolateral PFC (dlPFC), ventrolateral PFC, orbitofrontal cortex (OFC), dorsal anterior cingulate cortex (dACC) and the ventromedial PFC (vmPFC), which are associated with psychiatric illnesses including OCD.[52]

Much of our understanding of the complex anatomy of the ALIC i.e. where each cortical connection is localized within the bundle, is largely obtained from non-human primate tract-tracing studies. The human PFC and underlying white matter is disproportionately large in humans compared non-human primates, complicating comparisons.[53] As these invasive neuronal tracer methods cannot be performed in humans, MRI techniques such as diffusion tensor imaging (dMRI) have been the backbone of connectomic analyses in humans.[54]

Diffusion in this context means Brownian motion or thermally-driven random motion and characterized in dMRI by the effective diffusion tensor, which describes the magnitude and direction of water mobility in three dimensions.[55] Diffusion is restricted by tissue boundaries i.e. membranes so that diffusion in e.g. white matter is anisotropic. Calculating the diffusion tensor (D) in each voxel, using different gradient orientations, allows for delineating entire axonal trajectories.[54] Nonetheless, there are several caveats to dMRI fiber tracking, including the identification of false tracts and suboptimal coverage of small pathways or those with complex geometry.[56] Several methods to overcome these limitations are the development of a template averaged across a large number of subjects to facilitate fiber tracking and neuroanatomical expertise to resolve errors in the automated fiber tracking process.[56]

The development of normative connectomes i.e. atlases of average brain connectivity calculated from large cohorts of subjects have allowed for robust modeling and simulation in both empirical and theoretical studies.[56,57] Specifically for DBS studies, the use of normative connectomes will allow for pooling across centers and connectomic analyses in situations when pre MRI data is not routinely acquired preoperatively.

Aim of this thesis and current problems

The aim of this thesis is three-fold. The first part of this thesis was aimed at identifying fiber bundles associated with clinical response to DBS or GVC. The specific ALIC fiber bundle that modulates clinical response to DBS or GVC in treatment refractory OCD patients is not determined. Identification of a shared pathway associated with clinical response among different DBS targets, may prompt the WSSFN to establish DBS as a therapy for treatment resistant and severe OCD, and, ultimately, increase treatment effectiveness. The second part of this thesis was focused on the neuropsychological outcome of OCD DBS in order to identify a cognitive pattern that is associated with outcome or would (in part) help explain the functional mechanism of OCD-DBS. Further this part assessed the effectiveness, timing and procedural aspects of CBT after DBS with the aim to provide clinical recommendations. The third part focused on postoperative aspects of (OCD)-DBS patients including surgical and hardware related adverse events of DBS. Third, introducing DBS in OCD imposes new challenges such as committing patients to a lifelong implant at a younger age, and possible additional effects of first-line treatments after DBS As it is suggested that emerging indications such as OCD may be more prone to undergo DBS hardware related complications when compared to e.g. Parkinson's disease a direct comparison of adverse events between different indications may further highlight the safety of DBS in OCD.

Part 1- Anatomical considerations

Chapter 2 provides a detailed clinical description of our cohort of refractory OCD patients receiving VC/VS stimulation and associates treatment outcome with a specific white matter tract of the ALIC.

In **Chapter 3**, we reviewed findings as described in **Chapter 2** together with results OCD patients who underwent DBS targeting different targets e.g. STN and Bed nucleus of the stria terminalis (BNST) from multiple centers exploiting similar methodological connectomic approaches and propose a unified network that, when modulated, would alleviate OCD symptoms.

In **Chapter 4** we analyzed pre- and postoperative images of patients who underwent Gamma-knife Ventral Capsulotomy (GVC) with the aim to correlate lesion characteristics with symptom improvement. Normative diffusion MRI based tractography was used to determine networks associated with successful lesions.

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. **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, with the aim to DBS with the aim to provide clinical recommendations

Part 3 – Surgical aspects

In **Chapter 7** we assessed patients undergoing DBS related procedures between January 2011 and July 2020 to retrospectively inventorise Adverse Events (AEs), which allowed to determine the safety of OCD-DBS relative to other indications.

Chapter 8 provides 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. We applied a decision 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.

Chapter 9 provides a general discussion of all chapters.

Chapter 10 analyses the valorization and impact of on future research and clinical practice of the work presented in this thesis.

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Chapter 2

Ventral capsule/ventral striatum stimulation in obsessive-compulsive disorder: towards a unified connectomic target for DBS?

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Abstract

Introduction

Obsessive-compulsive disorder (OCD) is among the most disabling chronic psychiatric disorders and has a significant negative impact on multiple domains of quality of life. Deep brain stimulation (DBS) is a treatment option for severe therapy-resistant OCD.

Objective

To provide a detailed clinical description and treatment outcome analysis in a cohort of 8 refractory OCD patients receiving VC/VS stimulation with the intention to validate discriminating fiber bundles previously associated with clinical response.

Methods

The primary outcome measure (the Yale-Brown Obsessive Compulsive Scale, Y-BOCS) and secondary outcomes depressive symptoms, anxiety and quality of life were retrospectively analyzed. DBS leads were warped into standard stereotactic space. A normative connectome was used to identify the neural network associated with clinical outcome.

Results

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) was associated with Y-BOCS reduction. This fiber bundle connected the frontal regions to the subthalamic nucleus and was functionally identified as the hyperdirect pathway of the basal ganglia circuitry.

Conclusion

Our findings show that in VC/VS stimulation, the neural network associated with clinical outcome shows overlap with that of previously described for other targets namely the anterior limb of the internal capsula, the nucleus accumbens or the subthalamic nucleus, which supports the evolvement from the concept of an optimal gray matter target to conceiving the target as part of a symptom modulating network.

Key-words: Deep brain stimulation, Obsessive compulsive disorder, ventral capsule/ventral striatum, connectivity analysis

Introduction

Obsessive-compulsive disorder (OCD) is characterized by the presence of time consuming unwanted and disturbing obsessions (thoughts, urges or images) and/or repetitive behaviors or mental acts (compulsions) aimed at reducing or preventing anxiety or distress.[1] In this heterogeneous condition, various kinds of obsessions and compulsions exist, pertaining to five main dimensions; safety, symmetry including repeating and counting compulsions, contamination, repugnant obsessions concerning sex, violence and religion, and hoarding.[2,3] A range of interventions is effective in the management of OCD including cognitive behavioral therapy (CBT) and pharmacological therapy. A large body of evidence advocate on the use of selective serotonin reuptake inhibitors (SSRIs) and the tricyclic antidepressant clomipramine in the treatment of OCD, often used in combination with CBT.[4-6] However, up to a 40-60% of the patients remain treatment-refractory, commonly defined as a less than 25% reduction on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), which urges the need for alternative treatment strategies, such as electrical stimulation of subcortical structures e.g. by way of deep brain stimulation (DBS).[7-10] Based on both clinical and experimental studies several targets for stimulation are defined including the ventral capsule/ventral striatum (VC/VS), nucleus accumbens (NAcc), the subthalamic nucleus (STN), the anterior limbs of the internal capsule (ALIC), superolateral branch of the medial forebrain bundle (slMFB), medial dorsal and ventral anterior nuclei of the thalamus (MD/vANT), the inferior thalamic peduncle (ITP), the bed nucleus of the stria terminalis (BNST) and the anterior cingulate cortex (ACC).[9,11-15] Up to now, over 200 patients have been treated with DBS for OCD.[16] Regardless of the anatomical target, the treatment response seems to be highly variable with Y-BOCS reductions ranging from 8 to 97%. The response rate, defined as a reduction in Y-BOCS of 35% or more, is around 60% for the VC/VS target.[16] Also improvements in general quality of life and OCD associated depression have been described.[17] Only recently, *Baldermann et al. (2019)* showed that in patients receiving ALIC/NA stimulation modulating a frontothalamic fiber pathway was able to predict 40% of the variance in clinical outcome. This was later confirmed for the STN and the ALIC target in multiple cohorts.[18,19]

Here, we aim to constitute to the current OCD-DBS paradigm shift away from stimulation of focal specific gray matter targets toward modulating specific brain networks. The present study aimed at testing whether the same fiber bundles previously associated with clinical response can be confirmed in a previously undescribed cohort of 8 refractory OCD patients receiving VC/VS stimulation.'

Methods

Patients

In this retrospective cohort, 8 patients were selected for VC/VS stimulation between the period of 2014 – 2019 according to the indication criteria based on the criteria proposed by *Nuttin et al.*[20] These criteria included the diagnosis of severe OCD on the basis of DSM-5[1], with a Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score of at least 30/40. This level of symptoms should have persisted for a minimum of 5 years, despite adequate trials of, or intolerance for, two selective serotonin reuptake inhibitors and clomipramine, augmentation strategies (i.e., antipsychotic medications), and CBT. The patient had to be at least 18 years of age and able to provide for informed consent. Exclusion criteria were substance abuse, current or past psychotic disorder and co-morbidities that made the patient ineligible for surgery. Referred cases were reviewed in a multi-disciplinary DBS board. Patients were referred to an independent psychiatrist for a second opinion on whether all the criteria were met. See *table 1* for baseline characteristics.

Procedure

For a detailed description of our stereotactic DBS procedures, see also previous publications.[21-23] In short, all the surgical procedures were performed under general anesthesia with remifentanil and propofol. A Leksell stereotactic frame (Model G, Elekta Instrument Stockholm, Sweden) was mounted on the skull and a peri-operative CT-scan of the head with frame was acquired and fused with the pre-operative MR images using Framelink software (Medtronic, Fridley, USA). The planned target was the VC/VS with the stereotactic coordinates: (-) 6 lateral of the middle of the bi-commissural line (mid AC-PC), 12 mm anterior of the mid AC-PC and -3mm under the bi-commissural line. The target was adjusted based on the patient's individual anatomy. Typically, we planned a paraventricular trajectory, along which in the first three patients micro-electrode recording was performed. As the VC/VS area showed no typical extracellular electrical activity, micro-electrode recording was discontinued thereafter. All patients were finally implanted with bilateral quadripolar electrodes (Model 3387, Medtronic, Fridley, USA) along the central trajectory with variable contact points on target *(see table 2)* which were subsequently connected to an IPG (Activa PC, Medtronic, Fridley, USA)

Imaging, lead localization, estimation of the volume of tissue activated (VTA) and connectivity analyses

All subjects had a pre-operative 3-T MRI (Philips, Eindhoven, The Netherlands) or 1.5-T MRI in case of an implanted DBS system *(STN, baseline characteristics)*. The sequence used was a

Patient	Sex	Age onset (y)	Education*	Disease duration (y)	Axis I Comorbidity	Obsessions
1	Female	15	4	33	MDD	Perfectionism
2	Female	20	6	20		Fear of contamination
3	Female	22	6	31		Fear of contamination, Perfectionism
4	Male	13	6	22	MDD, ASD	Fear of harming others
5	Female	29	5	28	MDD	Fear of harm, contamination
6	Male	12	5	45	MDD	Need for order, cleanliness
7	Female	6	4	22		Fear of contamination, Fear of harming other
8	Female	17	5	35	ED: AN	Penance and reward

Table 1: Patient Characteristics

3DT1 (voxel size 1x1x1mm) with gadolinium. Post-operatively, a CT (Voxel size 1x1x1mm; Siemens, Erlangen, Germany) or a 1.5-TT1 MRI was performed to localize the DBS leads. DBS electrodes were localized using the Lead-DBS pipeline.[24] Post-operative CT- and MRimages were linearly coregistered to preoperative T1 images using Advanced Normalization Tools (ANT).[25] Subcortical refinement was applied (as a module in Lead-DBS) to correct for brain shift that may have occurred during surgery. Images were then normalized into ICBM 2009b Non-linear Asymmetric ("MNI") template space using the SyN approach implemented in ANTs, with an additional subcortical refinement stage. Both coregistrations and normalizations were visually reviewed and refined, if needed. DBS electrodes were then localized using Lead-DBS and warped into MNI space.[19] As a relative measure for targeting precision and electrode registration, preoperative target AC-PC coordinates were mapped into MNI space, where a distance of 2 mm was accepted as adequate.[26] The Euclidean distance between the contact point and the closest in the shell of the target structure was calculated using MATLAB (R2020a, Mathworks, Natick, Massachusetts). The volumes of tissue activation were estimated using a finite element method (FEM) with patient specific stimulation parameters, *see table 2.* Gray matter was defined by the CIT168 Reinforcement Learning Atlas.[27] Intersecting volumes of relevant gray matter structures within the CIT-168 atlas with VTAs were calculated with the Lead-DBS pipeline.

In order to validate discriminating fiber bundles previously associated with clinical response we adapted the methodology of Irmen *et al.*[19] Accordingly, based on a normative connectome,

	Medication History					
Compulsions	SSRI	Anti-psychotica	Clomipra-mine	Psycho-therapy	Previous DBS	Time to last follow-up (m)
Cleaning, Ordering, Checking	Venlafaxine	Aripiprazol		CBT	STN	74
Washing, cleaning	Paroxetine, Cipramil, Sertralin	Olanzapine, Risperidon		CBT		35
Cleaning, Counting, Checking	Sertraline, Citalopram, Duloxetine	Quetiapine	Yes	CBT		28
Mental compulsions, washing	Fluoxetine	Quetiapine	Yes	CBT		11
Mental compulsions, checking	Sertraline, Paroxetine, fluvoxamine		Yes	CBT		20
"Just-Right" behavior	Paroxetine, Venlafaxine, Amitriptyline		Yes	CBT		20
Cleaning, washing, checking, counting	Fluoxetine, Sertralin			CBT		12
cleaning, checking, exercise	Fluvoxamine, Paroxetine, Citalopram	Quetiapine	Yes	CBT		10

individual fibers were assigned a 'Fiber R-score' by correlating the fiber tract's connectivity to E-fields across patients with clinical outcome.[28] In short, a fiber tract that passes close to an active contact of patients with Y-BOCS improvement but far from active contacts in patients with Y-BOCS worsening would receive a high Spearman's R-value (and tracts exhibiting the inverse property received a highly negative R-value).[29] R-values were corrected for the stimulation amplitude. Validation of the tracts was sought by performing a k-fold cross prediction.[29,30]

Stimulation, Data collection and Statistical analyses

Typically, the monopolar stimulation of contact closest to target was turned-on at low voltage several days after implantation. During regular follow-up moments by the treating psychiatrist (AL) stimulation parameters were adapted (active electrode, pulse width, amplitude and frequency) based on clinical response and stimulation related side-effects. See table 2 for the active electrode and stimulation parameters at time of last follow-up. Patient characteristics, stimulation parameters, surgery or stimulation related complications and psychiatric assessments were retrospectively collected at baseline and at the time of last follow-up and included the Y-BOCS, the Beck Depression Inventory – II (BDI-II) , 3-level EQ-5D and the State-Trait-Anxiety-Inventory (STAI). [31-35] EQ-5D-3L outcomes were presented as a single global health index with a weighted total value, according to the Dutch population.[36] Responders were defined as patients with ≥35% Y-BOCS reduction at the time of last-follow up.

Clinical outcome variables, relative distances of active electrodes to atlas structures, VTA-atlas intersection volumes between non-responders and responders were compared using the Chi-squared test, Student's T-test or Mann-Whitney U where appropriate. The Kolmogorov-Smirnov was used to test for normality. P-values<0.05 were considered statistically. All statistical analyses were performed using IBM SPSS Statistics, version 20 (IBM Corp., Armonk, N.Y., USA).

Table 2: Target coordinates and Stimulation parameters

Patient	Target coordinates*		Active contacts		Amplitude	Pulse width (ms)	Frequency (Hz)
	Left	Right	Left	Right			
1	-7;12.8;-3	7;12.7;-3	C+, 1-	C+, 9-	7.5 mA	90	110
2	-6;14.5;-4	6;14.5;-4	C+, 2-	C+, 10-	5.5 V	90	130
3	-5.5;13;-3	6;12.5;-4	C+, 2-	C+, 10-	5.5 mA	150	130
4	-8;14;-1	7;13;0	C+, 0-	C+, 8-	3.5 mA	90	130
5	-7;12;-2	7;12;-2	C+, 0-	C+, 8-	7.0 mA	60	130
6	-6;14;-4	6;14;-4	C+, 0-	C+, 8-	5.0 mA	90	130
7	-6.5;13;-3	6;13;-3	C+, 3-	C+, 11-	8.2 V	60	130
8	-5.5;16;0.18	5.5;16;0.18	C+, 0-	C+, 8-	4.5 V	90	110

Notes: * Coordinates in native space; x, y, z from mid-ACPC.

Ethical statement

The work described was conducted in accordance with the Declaration of Helsinki. Approval by the institutional review board and patient consent were not required as the present study has no obligations to the Dutch Act of Scientific Research in Humans.

Results

We included 8 patients with a minimum duration of stimulation of 10-months and a median of 26 months. Five patients were considered to be a responder while 3 remained non-responsive, resulting in a response rate of 63%. The mean total Y-BOCS reduction was 10.5, with an equal reduction in Y-BOCS subscores for obsessions and compulsions, *see table 3.* Specified for responders, the mean total Y-BOCS reduction was 16.6. There were no significant differences in age at surgery, age at onset, sex, disease duration, time of follow-up, OCD severity, or the remainder outcome measures at baseline between responders vs. non-responders, *see supplementary table 1*.

Table 3: Clinical outcome

	Baseline [±SD]	Last follow-up [±SD]	Mean difference [95%CI]	p-value
YBOCS				
Total (8)	33.12 [3.34]	22.63 [7.91]	10.5 [2.88;18.13]	0.014
Obsessions (7)*	16 [1.63]	11 [1.63]	5 [0.44;9.57]	0.036
Compulsions (7)*	16.57 [2.07]	11.86 [3.98]	4.71 [0.2-;9.20	0.042
BDI-II (7)	29.71 [9.05]	21.43 [11.04]	8.28 [-5.39;21.96]	0.189
STAI (3)				
X1	59.75 [15.05]	42.33 [19.04]	13.67 [1.41;25.92]	0.041
X2	69.15 [7.05]	52.33 [22.03]	10.67 [-33.09;54.43]	0.404
EQ-5D (5)*				
Index	0.60 [0.14]	0.65 [0.29]	0.05 [-0.37;0.49]	0.686
EQ-VAS	41.6 [7.73]	63 [12.55]	-21.4[-33.93;-8.89]	0.009

SD: standard deviation; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; BDI-II: Beck Depression Inventory – II; STAI: State (X1)-Trait (X2) Anxiety Inventory; EQ-VAS: EuroQol- visual analogue scale

The STAI (X1) score for anxiety symptoms improved significantly (from 59.75 ± 15.05 to 42.33 ± 19.04, p = 0.041). The EQ-VAS as included in the EQ-5D was significantly better post-operatively compared to baseline. When translated categorically, the mean BDI-II scores clinically improved from clinically severe depression to moderate depression.

In a subsequent analysis, there were no significant differences in secondary outcome measures between responders vs. non-responders, *see table 4. We refer to supplementary table 2 for a detailed description of the observed complications within this cohort.*

Table 4: Clinical outcome Responders vs Non-responders

	Responders [±SD]	Non-Responders [±SD]	p-value
Y-BOCS	17.8 [5.41]	30.67 [1.53]	0.009
BD-II (7)	18 [14.99]	34 [9.45]	0.25
EQ-5D (5)			
Index	0.67 [0.30]	0.63 [0.30]	0.76
EQ-VAS	62.5 [12.58]	65 [12.58]	1

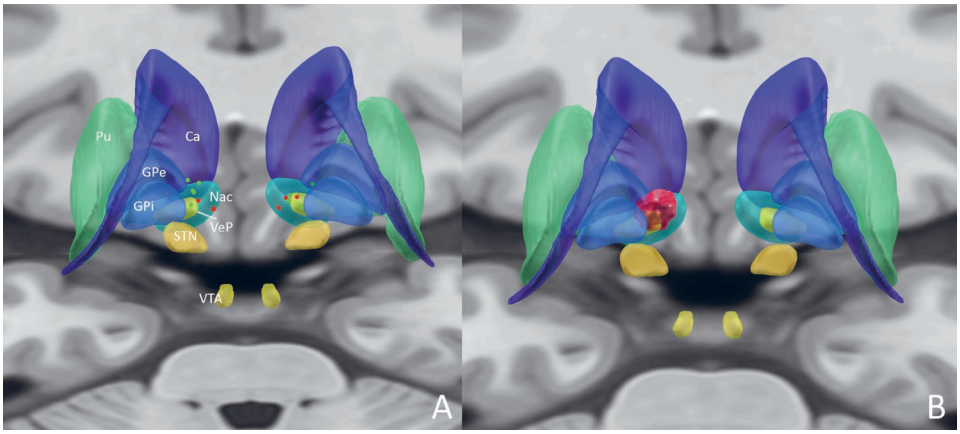

Figure 1: Note: P-A visualization. Localization of the active electrodes mapped in ICBM 2009b Nonlinear Asymmetric MNI template (A) and the %Y-BOCS reduction mapped on the Volume of Tissue activation for all patients, mirrored to the left side (B). Responders are shown in green, non-responders in red (A). Abbreviations; Pu: putamen; Ca: Caudate nucleus; GPe: external globus pallidus; GPi: internal globus pallidus; STN: subthalamic nucleus; VeP: ventral pallidum; VTA: ventral tegmental area; NaC: Nucleus accumbens

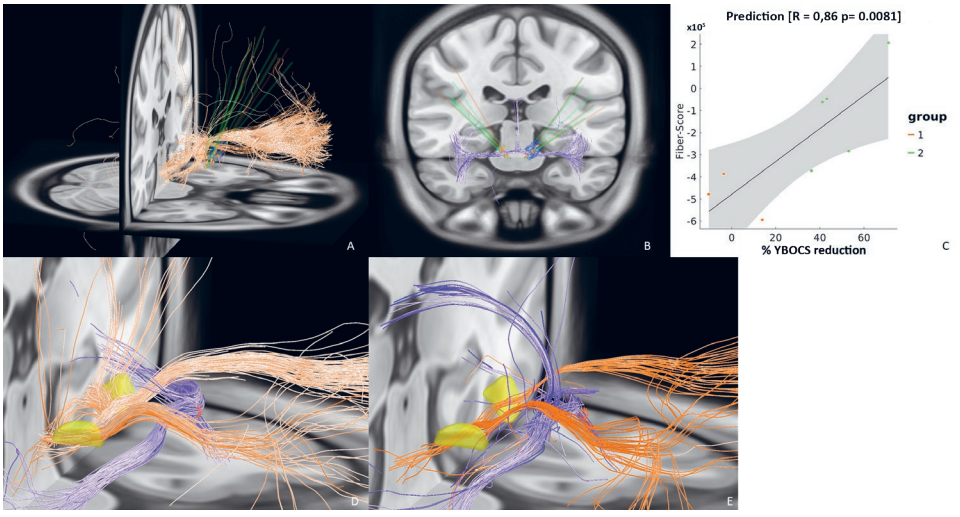

Figure 2. Left and middle; Positive (A) and Negative (B) predicting fibers associated with clinical improvement are shown in red and blue. Right. Correlation between the degree of stimulated positive predictive tracts and percentage Y-BOCS reduction (C). Gray shaded areas represent 95% confidence intervals. Group 1 represent non-responders, group 2 responders respectively. This analysis is based on a normative connectome. (D) The identified predicting fiber tracts as identified by Li et al as available in Lead-DBS. The subthalamic nucleus is depicted in orange. (E) Close-up of figure (A) and (B) combined.

Electrodes were successfully registered in MNI space, with 95% of the contact points closest to target within an Euclidean distance ≤ 2.0 of the target coordinate in MNI space.26 Figure 1a shows the anatomical location of the active electrode (table 2) during last follow-up in MNI space with gray matter defined by the CIT168 Reinforcement Learning Atlas. Visually inspected, it seems that the active electrode of non-responders show a more medial localization of the active contact points, especially on the left side, see figure 1a. However, the X-coordinate of the active electrode and the percentage of Y-BOCS reduction were not significantly correlated (Pearson's r=-0.61; p=0.10). Furthermore, no significant correlations were found between relative distances of active contact points with gray structures, as provided by the CIT168 Reinforcement Learning Atlas, and the percentage in Y-BOCS reduction.
There was no significant difference in the mean pooled VTAs between responders (424 mm3 [± 255]) and non-responders (370 mm3 [± 158]), (p=0.754). The intersecting volumes between the CIT-168 gray matter structures and the VTAs were calculated. VTAs intersected with 9 out of the 16 structures in the atlas. None of the intersecting volumes significantly correlated with the percentage Y-BOCS reduction. *see supplementary table 3*.

In an attempt to validate the results of Li *et al.* which identified a subtract of the anterior limb of the internal capsule, connecting the prefrontal cortex to the subthalamic nucleus and the mediodorsal nucleus (MD) of the thalamus positively associated with Y-BOCS reduction, we acquired a similar methodology as provided in Lead-DBS. Fiber R-values to E-fields were assigned across patients with clinical outcome as performed in *Irmen et al* [29], *see figure 2*.
Unthresholded discriminating fiber tracts were identified which show a great overlap with the fiber tracts observed by Li et al. Using subsequent prediction analyses using k-fold cross validation (K=2) the degree of lead connectivity was strongly correlated with Y-BOCS reduction (r=0.76 at p=0.011). However, also seemingly irrelevant tracts were identified, specifically tracts in the corpus callosum and in the temporal cortices, *see supplementary figure 1*. Increasing the threshold of the tracts to be connecting if the E-field magnitude >100.3V/mm and >22% of the E-fields, disregarded these irrelevant tracts but preserved the fiber tracts graphically similar to Li et al, see figure 2. The fiber bundles negatively associated with the percentage Y-BOCS reduction are recognized as the posterior limb of the anterior commissure, connecting the bilateral temporal cortices and cingulate fiber bundles. The positive discriminating fibers connect the prefrontal cortex with the STN. In a subsequent prediction analyses using k-fold cross validation (K=2) the degree of lead connectivity was strongly correlated with clinical outcome (r=0.86 at p=0.008).

Discussion

Our analysis supports that a subpart of the ALIC, that connects areas of the prefrontal cortex with the subthalamic nucleus and medial (MD) nucleus of the thalamus, is associated with optimal clinical response in a cohort of 8 patients receiving VC/VS stimulation for refractory OCD. With regard to the validity of clinical outcomes, the mean reduction in Y-BOCS score of 31.7% is somewhat less favorable compared to the large cohort of Denys *et al.* (40%, SD=9.4), lower than a large international prospective trial by Ménchon *et al.* (20% SD=9.5).[37-39] but within the confidence interval reported in the meta-analyses by Alonso *et al.* (45.1%, 95% CI = 29.4% to 60.8%) Compared to Denys *et al.* and Alonso *et al.* we report a similar responder ratio (60% and 52% respectively). As previously reported, a beneficial effect on state anxiety was observed.[15,40]

The mean EQ-5D health index is within the confidence interval the EQ-5D (0.67 CI = 0.64 to 0.70) of large cohort of chronic and demographically comparable OCD patients.[41] We did not observe an improvement in quality of life as observed in Ménchon *et al.* This may indicate that other factors than OCD severity contributed to the quality of life outcome, or reflect the lower sensitivity and precision of the EQ-5D-3L in our study compared to the EQ-5D-5L used by Menechon *et al*.[42] Mood improved in both responders and non-responders, without significant between-group differences, showing that effects of mood may be independent of effects on OCD symptoms.

Using the 2-fold cross-validation method, we were able to validate the identified fiber tracts in our cohort. Of note, this correlation is somewhat circular and meant to describe the degree of how well discriminative tracts could explain the same sample of patients on which they were calculated. We were able to show these positive and negative fiber tracts with a relative low number of patients receiving a stimulation of a different target (VS/VS) compared to the four cohorts in which overlapping fiber bundles were originally identified, which either addresses pitfalls in methodology of using human scale diffusion weighted MRI images (DWI), a normative connectome, statistics and accuracies in lead localization which may result from the approach of warping electrodes into common space or cautiously validates the robustness of the findings. Without elaborating on the above standing technical issues, we would like to note that using a normative connectome, as provided by the well validated neuroimaging pipeline of Lead-DBS, has abled further examination of stimulation effects, as patient specific DWI data was lacking in our cohort. However, in order to be clinical applicable, or to have an impact on stereotactic planning, these tracts have to be identified in native patient space. Individual anatomical variability of orbitofrontothalamic tracts has been observed, which may in turn partially explain for variation in treatment response.[43]

The tract associated with good clinical outcome in the present study was identified as a subpart of the ALIC that connects areas of the prefrontal cortex with the subthalamic nucleus and medial (MD) nucleus of the thalamus.[19] Functionally, this tract is recognized as the hyperdirect pathway to the STN originating from the dorsal anterior cingulate cortex

and the ventrolateral prefrontal cortex traversing within the ALIC, implicating the involvement for the limbic cortico-basal ganglia-thalamocortical circuit.[19] The role of the hyperdirect pathway within this circuit may be explained by the hypothetical 'pulley competition model'. In this model it is suggested that the direct and indirect pathways compete throughout the BG, with the strength of each pathway acting as weights on opposing sides of a pulley. When activation of the direct pathway overpowers that of the indirect pathway, it results in facilitation or a concrete action if the difference exceeds a critical threshold.[44] In this model, the role of the hyperdirect pathway is that of a brake that can cancel an action before the activation that leads to it reaches the critical threshold.[44] Modulation of the hyperdirect pathway could thus result in a direct inhibition of the dACC's direct pathway. Hyperactivation of the dACC is observed in OCD, both at rest and during symptom provocation and may mediate the elevated fear and anxiety associated with OCD.[45-47] Another role for the dACC in OCD may be recognized when introducing Hierarchical Reinforcement Learning (HRL), within its pathobiology. HRL is a machine learning paradigm that is increasingly used in behavioral sciences to explain normal and abnormal behavior. Within the HRL model, the anterior cingulate cortex instigates a specific task appropriate to the environmental situation and subsequently instructs the actor module to perform this task. The dysfunctional behavior observed in OCD may emerge from a faulty task or option selection by the ACC, which ultimately is corrected by activation of the hyperdirect pathway by DBS (Bouwens van der Vlis et al, submitted).

Our clinical findings should be interpreted within the limits of this small-sized retrospective open case study, lacking randomization and non-blinded assessment which may therefore be prone for systematic bias. Further, patients had continuous medication and psychotherapy during the follow-up of the study. Therefore, a synergistic or confounding effect of co-treatment cannot be ruled out.

Taken together, the present study contributes to the available literature of VC/VS DBS as an effective and well tolerated treatment option for patients with refractory obsessive-compulsive disorder and supports the finding that specifically modulating the limbic circuit is associated with treatment response. The latter fits the evolution from the search for a single, optimal gray matter target towards the conception of modulating networks that support particular symptom profiles. Expanding the connectomic analyses to targets which are not part of the classical cortico-basal ganglia-thalamocortical circuitry i.e. the ITP and the BNST, could reveal other differentiating brain networks. Finally, well-controlled randomized studies in larger samples are needed to address clinical variability, including analyses of individual white matter tracts.

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Supplemental material

Supplementary table 1: Baseline measures responders vs. non-responders

	Responder [±SD]	Non-responder [±SD]	p-value
Sex (m;f)	1;4	1;2	0.67
Age at onset (y)	15.2 [±6.3]	19.33 [±8.74]	0.46
Age at surgery (y)	41.2 [±10.37]	55.33 [±2.89]	0.066
Time to last follow-up (m)	32.0 [±25.65]	16.67 [±5.77]	0.36
Y-BOCS			
Total	34.4 [±2.30]	31.0 [±4.36]	0.19
Obsessions	16.8 [±1.79]	16.67 [±2.08]	0.44
Compulsions	17.60 [±1.14]	15.33 [±2.52]	0.412
BDI-II	29.5 [±11.09]	30.0 [±7.81]	0.95
EQ-5D			
Index	0.58 [±0.19]	0.63 [±0.08]	0.763
EQ-VAS	43.3 [±10.41]	40.0 [±0]	0.615

2. Complications

Two major complications were reported in this cohort. Several years before VC/VS implantation, patient 1 received STN stimulation for OCD. However this procedure was complicated by a severe wound infection probably due to compulsive cleaning of the surgical area, for which the internal pulse generator had to be ultimately removed. After IPG re-implantation, therapeutic stimulation parameters were never reached due to severe motor-side effects i.e. coordination and balance deficits after which it was decided to switch to VC/VS stimulation. Other minor hardware- and stimulation-related side-effects are shown in table 5. 4/8 of patients report transient complaints of hypomanic symptoms e.g. typical mood-disturbances and sleep deficits during gradual stimulation increments.

Supplementary Table 2: Complications

	Major	Minor
Surgery/Hardware related		
ICH	-	-
Infection	1	2
Mechanical		1
Stimulation related		
Psychiatric	-	4*
Neurologic	1	-

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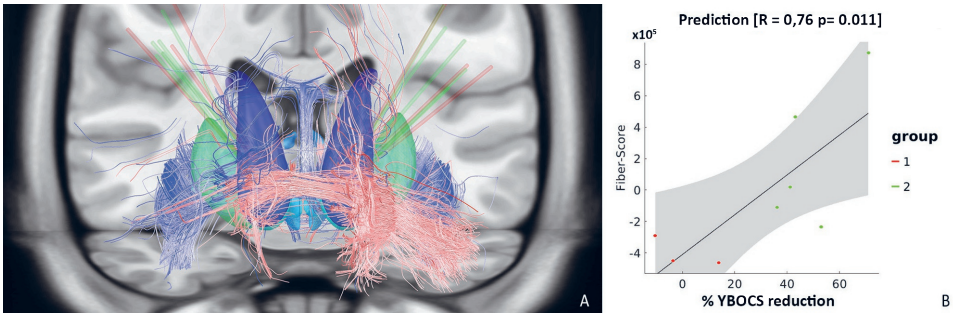
Notes: Mechanical complication: prolonged pain after IPG replacement. * Hypomanic episodes

3. Unthresholded discriminative fiber tracts.



Supplementary figure 1. Unthresholded discriminative fiber tracts.

4.Volumes of intersection between VAT and target structures correlated with clinical outcome.

Supplementary Table 3: Correlation atlas intersection volumes and clinical outcome

	Right (r)	p	Left (r)	p
Atlas structures				
Putamen	0.35	0.19	0.41	0.182
Caudate nucleus	-0.04	0.478	-0.05	0.43
External globus pallidus	0.31	0.23	0.14	0.367
Internal globus pallidus	0.43	0.143	0.26	0.274
Subthalamic nucleus	-0.04	0.476	-0.03	0.482
Ventral pallidum	0.33	0.224	-0.43	0.144
Nucleus accumbens	0.05	0.485	-0.6	0.059
Hypothalamus	0.38	0.194	-0.6	0.072
Extended Amygdala	0.29	0.244	-0.26	0.277

Notes (r): correlation coefficient.

Chapter 3

Connectomic deep brain stimulation for obsessive-compulsive disorder

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Abstract

Obsessive-compulsive disorder is among the most common and disabling psychiatric disorders. Although deep brain stimulation can be an effective treatment, it is not fully clinically established. This is, at least in part, due to ambiguity about the ideal target and insufficient knowledge about underlying mechanisms.

Recent advancements suggested that changes in broader networks, instead of local impact at the stimulation site, 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.

In this critical review, 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. 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.

Introduction

Deep brain stimulation (DBS) for obsessive-compulsive disorder (OCD) is recommended for severely affected and treatment-refractory cases in practice guidelines for OCD worldwide (1) but still not considered a fully-established therapy (2). This is at least in parts due to uncertainty about the precise brain networks to modulate for optimal treatment response. The anatomical and functional characterization of circuits that, when stimulated, reduce obsessions and compulsions could enhance efficacy and thus improve the risk-benefit profile of DBS as well as provide testable hypotheses for neuromodulation of OCD in general.

Remarkably, different DBS target sites have shown comparable response rates in OCD (3, 4). Prior work demonstrating that DBS for OCD exerts clinical effects beyond the local/focal stimulation target (5, 6) has motivated the concept of a broader, potentially shared neural network responsible for improvement of obsessions and compulsions. In parallel, OCD is a heterogeneous disorder with evidence suggesting that a varying profile of multiple networks may be affected in each patient and thus relevant for neuromodulatory treatment (7). Connectomic DBS is a rapidly developing neuroscientific concept that can help to understand how different target regions contribute to clinical improvement via linked networks. In this critical review, we aim to scrutinize methodologies and findings from connectomic studies and DBS interventions for OCD to identify common and diverse pathways likely to be effective for reducing obsessions and compulsions. With this aim in mind, several centers, including the MUMC+, collaborated and shared data. We focus on structural connectivity for the sake of conciseness; relevant functional MRI (fMRI) studies in OCD DBS (5, 8–10) are discussed where appropriate. For the purpose of this review, we chose the words "predict" or "cross-predict" as shorthand for situations where a model was calculated (i.e., trained) on data to explain variance in clinical outcomes observed *independent* (i.e., unseen) datapoints. This mainly involves cross-predictions made with the central ALIC pathway published in the studies by two studies (11, 12) and could involve cross-validations (e.g. leave-one-out, split-half or k-fold cross-validations), but also replications in independent test-cohorts. More rigorous guidelines to establish prediction have recently been published (13). We demonstrate that the central claim made in this review would largely fulfil these guidelines by supplementary figure S1.

From focal targets to interconnected networks

The idea of modulating a network (instead of a focal brain region) with surgery is not new. Around 1950, Jean Talairach and Lars Leksell independently began lesioning the anterior limb of the internal capsule (ALIC), with the aim of *disrupting a network* between limbic and prefrontal regions (14). In particular, patients suffering from OCD improved after ablations of the ALIC (capsulotomy) or the anterior cingulum (cingulotomy) (15, 16). Following this work, the first target used for DBS in OCD was the ventral ALIC (17), gaining approval by

the U.S. Food and Drug Administration under a Humanitarian Device Exemption in 2009 and CE-marking by the European authorities. In the following years, different nuclei adjacent to the ALIC, including the ventral striatum (VS) containing the nucleus accumbens (NAc) as well as the bed nucleus of the stria terminalis (BNST), have been proposed as key regions for successful DBS (18, 19). Through empiric evidence from DBS in movement disorders, other brain targets such as the subthalamic nucleus (STN), the inferior thalamic peduncle and the superolateral branch of the medial forebrain bundle (MFB; later referred to as ventral tegmental area projection pathway (20) or midbrain target (21)) have been successfully targeted in OCD (22–24). Remarkably, modulation of these distinct subcortical targets (Figure 1) all show the potential to improve obsessions and compulsions, already pointing towards a common network responsible for clinical efficacy. Using modern MRI technology such as diffusion-weighted imaging based tractography (dMRI), we are now poised to create realistic *in-silico* models of how these different sites of intervention may form nodes that assemble a common network (Figure 2). Specifically, by mapping clinical effects onto modulated neural pathways, researchers have now begun to identify optimal connectivity profiles associated with clinical efficacy (25). "Undeniably, classic analysis of optimal spots can further complement such network analysis to characterize or validate specific hubs (i.e. for surgical targeting) within a given network. Specifically In the case of DBS for OCD, network analysis is of interest, given that different target regions have yielded comparable clinical improvements, suggesting a commonly modulated network. **Box 1** outlines different methodological approaches that have been used in OCD-DBS so far.

Text Box 1: Different approaches have been developed to study pathways associated with clinical response to DBS. A general discussion of the methodological approaches is given in the supplement. For a brief overview, the following methods have been used in patients with OCD:

Approach A) *Tract- / pathway-activation models* (TAM/PAM): This approach models individual axonal pathway activation (26) by placing axonal models alongside a priori defined and established anatomical fiber tracts. The axonal response of these pathways to DBS is then estimated based on electrode location and stimulation parameters. The resulting pathway profiles can then be assigned to clinical outcome of OCD (e.g. 25)

Approach B) *Spatial pathway dependency*: This method calculates spatial dependencies (e.g. *distance*) of stimulation sites or VATs with predefined pathways from tractography. Clinical outcomes can then be assigned to the respective spatial dependency (e.g. 26).

Approach C) *Activation volume tractography* (AVT): Streamlines are filtered that traverse VATs as the seed region from either a finite set of tracts (29) or whole-brain connectomes (30). The resulting individual stimulation-dependent connectivity profiles can then be matched with the clinical outcome for group analysis using the following approaches:

1) *DBS network modeling*: Assessment of voxel-by-voxel association of connectivity estimates and clinical outcome (e.g. regression analysis) (e.g. 29, 43)
2) *Fiber filtering* or *discriminative tractography*: Assessment of a tract-by-tract analysis comparing outcomes of patients with and without a specific fiber tract modulation (11, 12, 31–33)

Connectomic studies of deep brain stimulation for OCD

In a first connectomic approach towards DBS for OCD, Hartmann et al. (27) investigated six patients who underwent DBS to the ALIC/NAc region employing tract activation modeling (Approach A in Box 1). The authors used a normative dMRI brain atlas to simulate the activation of fiber tracts placed along streamlines estimated by probabilistic tractography from each voxel of the seed region. In two responding patients, stimulation particularly affected fibers reaching the right anterior middle frontal gyrus (corresponding to the dorsolateral prefrontal cortex; dlPFC) with less influence on temporal lobe, superior frontal gyrus, amygdala, and accumbens area. Non-responders showed the largest number of activated fibers reaching the right thalamus and lateral orbitofrontal cortex (OFC). The authors concluded that targeting right dlPFC fibers leads to optimal response while negative outcomes resulted from wide-spread activation of non-therapeutically relevant fibers. While the latter conclusion (i.e. negative outcome associated with wide-spread activation) was not directly replicated in further studies discussed below, the study also suggested that modulation of a more centrally/dorsally rather than ventrally located white matter pathway within the ALIC was associated with optimal treatment response.

Liebrand et al. (28) investigated 12 patients with DBS in the ALIC/NAc region (Approach B in Box 1). Here, using individual preoperative dMRI, the authors manually predefined two fiber tracts hypothesized to carry out therapeutic effects – the anterior thalamic radiation (ATR) and the supero-lateral branch of the MFB. Both fiber bundles were presumed to traverse the ALIC based on previous studies (34) and were reconstructed using probabilistic tractography with the anterior thalamic nucleus or the ventral tegmental area as seed regions, respectively, and the ventral ALIC as waypoint. Proximity of the active electrode contacts to the boundaries of both fiber bundles were calculated, and the ratios between the two values were correlated with individual DBS outcomes. Authors observed a significant positive correlation between clinical improvements and the proximity ratio in favor of the MFB compared to the ATR. We note the nomenclature and conceptualization of this fiber tract, here identified as the MFB, has since evolved (21) and that the original authors now refer to this structure as the ventral tegmental are projection pathway (vtaPP) (20) while others refer to the respective brain stem target as a midbrain projection (21) (see below for a detailed discussion).

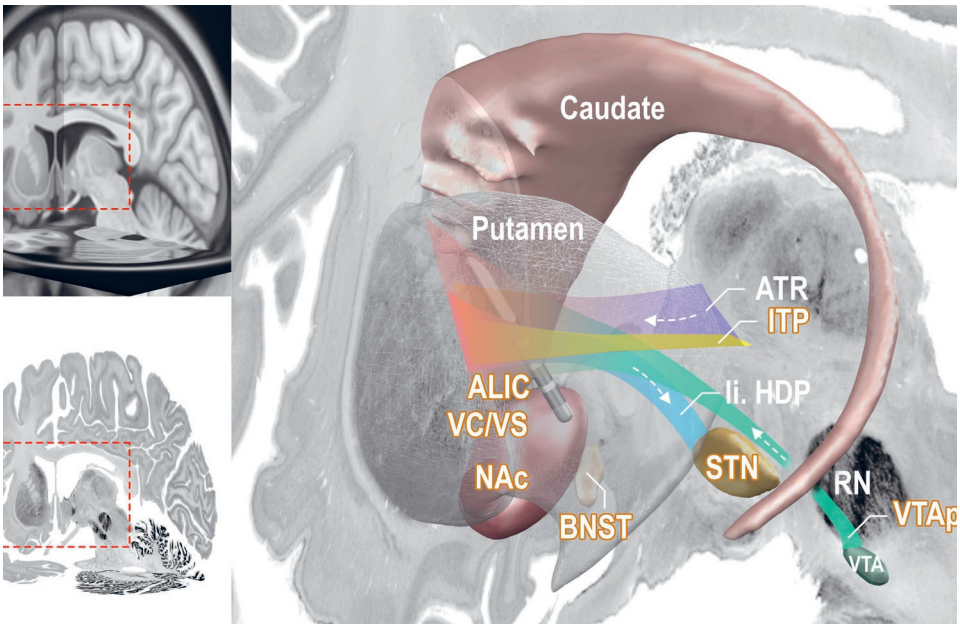


Figure 1: Different surgical DBS concepts for OCD and surrounding structures. Tracts traversing the anterior limb of the internal capsule (ALIC) (ATR = Anterior thalamic radiation; li. HDP = limbic/associative hyperdirect pathway) have been added schematically. Structures that have been targeted by DBS are outlined in orange. Please note that the aim of the figure is to outline surgical concepts that have been proposed in the literature. As discussed in this review, some are built on conflicting theories and thus may not be necessarily anatomically/mechanistically plausible. Left panels show inset relative to the whole brain for orientation on the T1 MNI 2009b (8) and BigBrain (9) templates. VC/VS = Ventral Capsule /Ventral Striatum, NAc = Nucleus Accumbens, BNST = Bed nucleus of Stria Terminalis, VTApp = Ventral tegmental area projection pathway (formerly superolateral branch of the medial forebrain bundle); RN = red nucleus; ITP = Inferior thalamic peduncle.

Using a different methodological approach (Approach C1 in Box 1), Baldermann et al. investigated a cohort of 22 subjects that underwent DBS to the ALIC/NAc region for OCD (11). Optimal voxel-wise structural connectivity profiles were calculated based on individual dMRI data in a subgroup of ten patients and based on normative dMRI data for another twelve patients. The resulting maps constituted models of optimal connectivity capable to *cross-predict* the outcomes in patients of the other subsample. This indirectly highlighted that employing individual and normative dMRI data alike would lead to meaningful models with predictive utility. To increase validity and power of the analysis, the whole sample was then analyzed using the normative connectome data across the whole group to calculate a map of optimal connectivity powered by an N of 22. This map revealed that connectivity between stimulation sites and both lateral and medial prefrontal cortices significantly predicted clinical outcomes across the cohort in a leave-one-patient-out cross-validation. Last, a fiber-

centric analysis (approach C2 in Box 1) was introduced to further determine the subcortical representations of this beneficial connectivity profile. This analysis revealed a fiber-bundle that connected the lateral and medial prefrontal cortex with the thalamus and STN which traversed the ALIC centrally, and dorsal to the NAc.

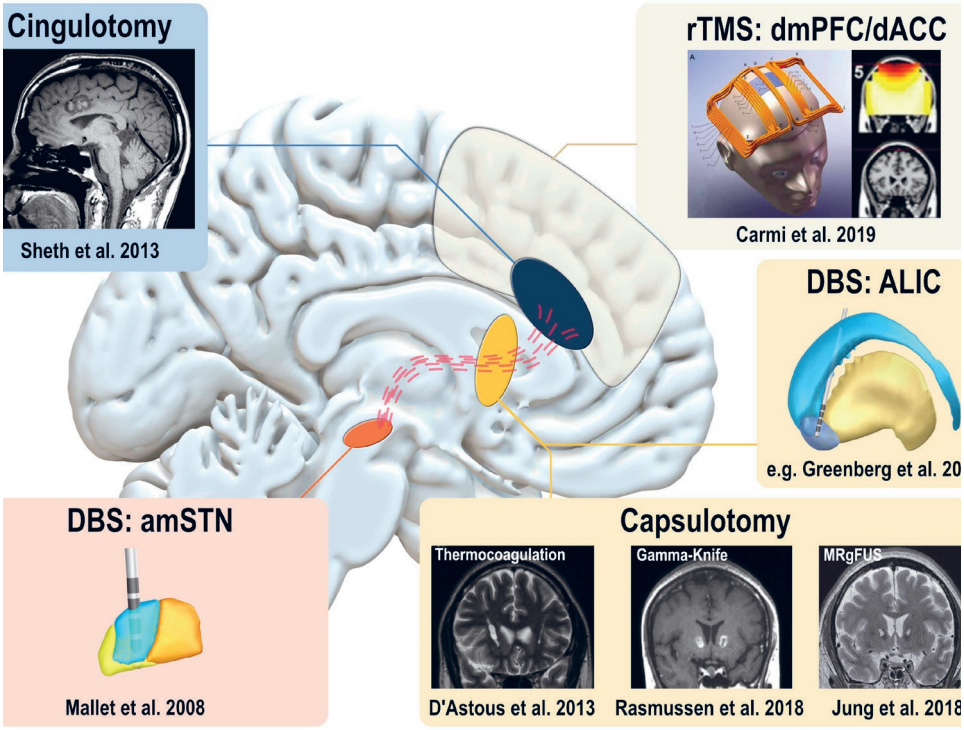
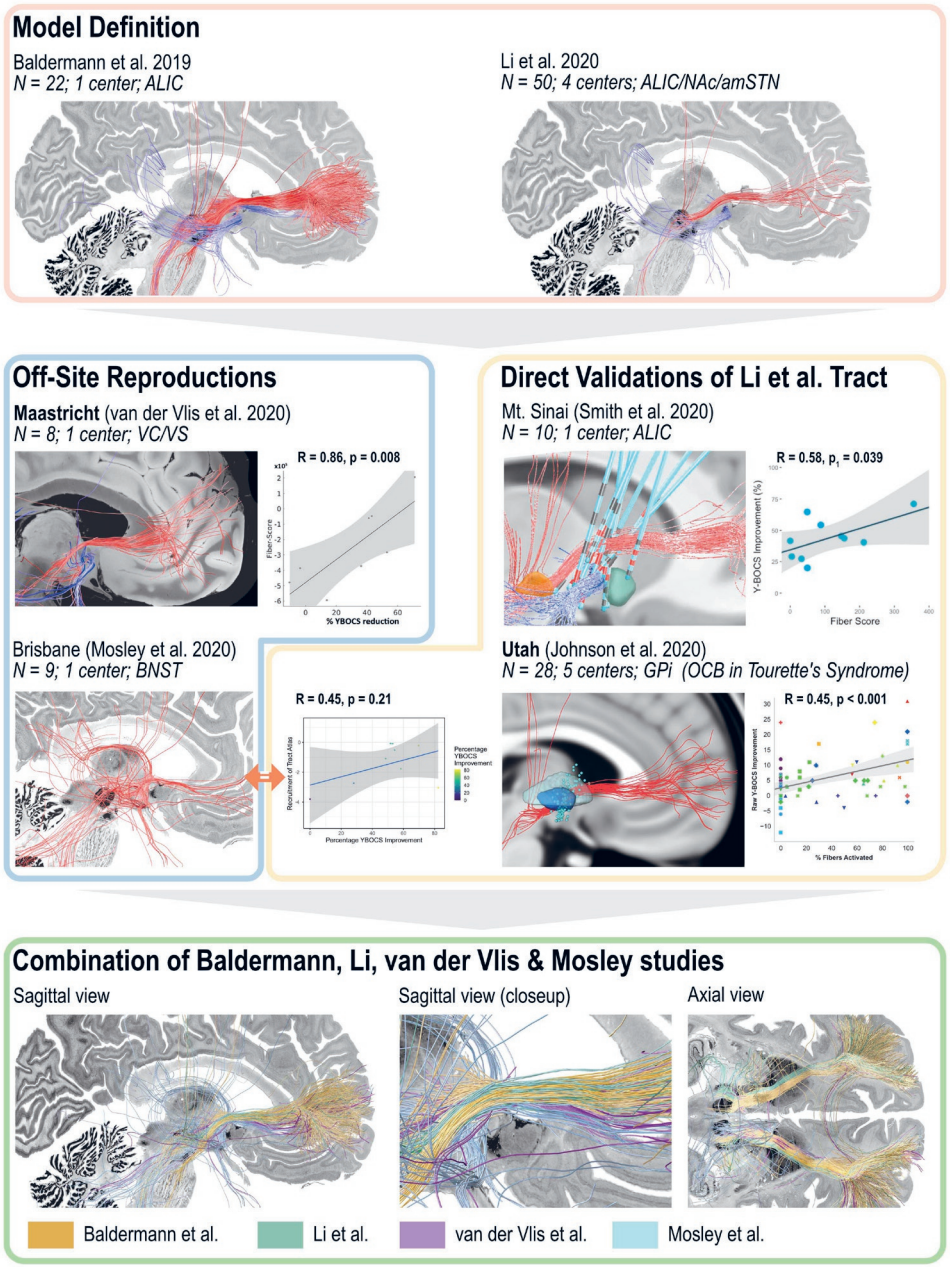


Figure 2: Effective neuromodulative treatments for obsessive-compulsive disorder (OCD) with schematic display of target regions. Existing target regions may give additional clues about a common pathway for treating OCD. Currently, the U.S. FDA approves two interventions: An H-coil transcranial magnetic stimulation (TMS) system targets the dorsal anterior cingulate cortex (dACC) and dorsomedial prefrontal cortex (dmPFC) (22) and deep brain stimulation of the anterior limb of the internal capsule (ALIC) (23). Another target for deep brain stimulation, the anteriomedial subthalamic nucleus (amSTN) showed efficacy in patients with OCD in a randomized controlled clinical trial (24). Meta-analysis of observational studies involving capsulotomy (25–27) and cingulotomy (28) show efficacy in severe OCD as a last-resort treatment (12), although controlled studies are lacking. All panels reproduced, with permission, from original work. Panel rTMS reproduced from (75). Panel by Jung 2017 distributed under the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0).

Further developing this novel approach (C2) – which has since been termed *fiber filtering* or *discriminative tractrography* – Li et al. published the largest study (N = 50) to date to determine connectivity associated with response to DBS for OCD (12). Initially, two samples with two different target regions were included. First, the same sample employed in the aforementioned study (11) was included (ALIC/NAc target). Second, a cohort of 14 subjects who received DBS to the STN was added. Results were validated by calculating the tract model on the first cohort and cross-predicting outcomes in the second (and vice versa). Finally, two smaller samples from independent centers (N = eight targeting the NAc and N = six targeting the ALIC/NAc region and STN in a crossover trial (35)) were used to further validate results. By doing so, the hypothesized pathway for OCD-DBS was refined, showing again that streamlines connecting the lateral and medial prefrontal cortex with the anteromedial STN and medial dorsal (MD) nucleus of the thalamus were predictive of successful DBS. A more conservative analysis of the data using a tractography atlas of basal ganglia pathways (which is less prone to false positives) identified a fiber bundle connecting the dACC with the STN via the ALIC as the strongest candidate tract represented by the atlas. After consultation with four anatomists, the tract was classified to represent a specific subsection of the ALIC, and could functionally include frontal hyperdirect input to the non-motor STN.

The resulting tractographic profile (12) was made publicly available as a reference for scientific use – both to further validate or falsify results and to compare it in three-dimensional fashion with competing results (Figure 3, top right). Indeed, an independent research group confirmed the predictive value of the published pathway in a sample of N = 10 subjects with OCD and DBS of the ALIC/VS applying the same analysis procedure (32). A second group re-calculated an optimal tract using the same methodology on a novel sample of N = eight patients and identified the same bundle in direct comparison to the published one (33). The significant association between clinical improvement and the extent of pathway modulation was reproduced in both replication studies (32, 33).


Model Definition
Baldermann et al. 2019
N = 22; 1 center; ALIC
Li et al. 2020
N = 50; 4 centers; ALIC/NAc/amSTN
Off-Site Reproductions
Maastricht (van der Vlis et al. 2020)
N = 8; 1 center; VC/VS
R = 0.86, p = 0.008
Fiber-Score
% YBOCS reduction
Brisbane (Mosley et al. 2020)
N = 9; 1 center; BNST
R = 0.45, p = 0.21
Recruitment of Tract Atlas
Percentage YBOCS Improvement
Direct Validations of Li et al. Tract
Mt. Sinai (Smith et al. 2020)
N = 10; 1 center; ALIC
R = 0.58, p1 = 0.039
Y-BOCS Improvement (%)
Fiber Score
Utah (Johnson et al. 2020)
N = 28; 5 centers; GPi (OCB in Tourette's Syndrome)
R = 0.45, p < 0.001
Raw Y-BOCS Improvement
% Fibers Activated
Combination of Baldermann, Li, van der Vlis & Mosley studies
Sagittal view
Sagittal view (closeup)
Axial view
Baldermann et al.
Li et al.
van der Vlis et al.
Mosley et al.

← **Figure 3: Summary of findings reported in Baldermann et al. 2019 and Li et al. 2020 (top) as well as off-site confirmations from additional studies (bottom).** Modulating red fibers was associated with optimal improvements while modulating blue fibers associated with poor response along the Y-BOCS score in respective studies. While some studies used the published dataset from the Li et al. study to cross-predict variance in outcomes in their patients (yellow box), others calculated a novel tract using the same method and graphically compared results (van der Vlis et al. study) or did both (Mosley et al. study). Note that the study by Johnson et al. investigated patients with Tourette Syndrome and comorbid obsessive-compulsive behavior (equally measured by the Y-BOCS score). The green box shows a direct overlap of results from the studies by Baldermann, Li and Mosley, respectively. In direct synopsis, the tract calculated by Mosley et al. traversed more ventrally. However, when overlaying their VATs with the tract calculated by Li et al., this was positively associated with clinical improvement (albeit not significantly). ALIC = anterior limb of internal capsule; Nac = Nucleus accumbens; amSTN = anteromedial subthalamic nucleus; VC/VS = ventral capsule/ventral striatum; BNST = bed nucleus of stria terminalis; GPi = globus pallidus internus; OCB = obsessive-compulsive behavior. Panel by Smith et al. reproduced, with permissions, from the original publication (other panels show original content).

Another recent report applied connectomic analyses to study a cohort of 9 OCD patients undergoing DBS targeting the BNST (31). Employing a voxel-by-voxel analysis of connectivity associated with clinical outcome, structural connectivity to the right vlPFC and hippocampal regions, but also to parietal and dorsomedial prefrontal areas significantly explained variance of response to DBS. A complementary fiber filtering analysis analogue to (12) revealed, among others, white matter fibers within the ALIC that connected the stimulation site to the midbrain, traversing the BNST onwards to the right vlPFC. This tract again graphically matched the pathway identified in (12) with a slightly more ventral course and overlap with the *originally* published tract (12) correlated with clinical outcomes to a similar degree – albeit not significantly ($R = 0.45$ at $p = 0.21$; $N = 9$). Lastly, a recent investigation of 28 patients with Tourette Syndrome treated with DBS to the globus pallidus internus (GPi) showed that modulation of the pathway published by (12) was also significantly predictive of improvement in obsessive and compulsive symptoms in these patients (36). This observation is remarkable since it suggests that DBS for OCD might act via symptom-specific rather than disease-specific networks. Specifically, it shows first evidence that the same network modulation approach could be effective transdiagnostically. Figure 3 summarizes the initial findings (Baldermann & Li studies) and confirmatory results (Smith, van der Vlis, Mosley & Johnson studies).

It is important to note that some of the quoted studies also highlighted additional pathways with functional relevance, i.e. directly dorsally (32) or ventrally (31) located to the tract published by Li et al (12) or connections between the amygdala and the BNST (31). As the respective authors rightly stated (32), a putative network associated with DBS response in OCD is likely *not restricted* to the already identified pathway but rather involves further

connections yet to be uncovered. As a further potential circuit, it has been shown that switching off DBS to the ALIC/NAc interferes with limbic connectivity between the vmPFC and the amygdala which linked to acute changes in anxiety and depression (8). This is in line with changes in mood symptoms after ALIC/NAc DBS which could be linked to more ventrally located streamlines connecting the vmPFC (11). Thus, this loop may explain changes in affective states and may further contribute to subsequent improvement of obsessions and compulsions (Figure 7). Along studies involving structural connectomics, there is a growing body of literature on changes in metabolic, functional, or electrophysiological activity in the brain during DBS for OCD that is worth mentioning here. A^{15}oxygen positron emission tomography (PET) by Dougherty et al. revealed an acute perfusion increase within the dACC and basal ganglia during ventral ALIC/NAc stimulation which correlated with improvement of affective symptoms (37), while Suetens et al. reported a decreased metabolism with active DBS in the ACC, inferior, middle and frontal gyri (38). In this study, capsulotomy for OCD resulted in an analogue reduction in metabolic activity in the ACC. Figee et al. reported a DBS-induced reduction in hyperconnectivity with the ACC and lateral prefrontal cortex seeding from the nucleus accumbens which was associated with greater reduction of obsessions and compulsions (5). A later study performed a ROI-based analysis of directional functional connectivity, showing that active DBS increased the impact of the vmPFC on an amygdala-insula network along improvements in depression and anxiety symptoms (8). Moreover, there is a number of electrophysiological studies showing that active DBS of the ALIC/NAc interferes with low frequency oscillations within the mPFC/ACC which can be linked to improvements in obsessions and compulsions (5, 6, 39) and cognitive performance during conflicts (here, DBS increased theta power in mPFC and vlPFC in patients with OCD and depression) (40). The role of ACC mediated cognitive performance during conflict in neuromodulation for OCD is further supported by data from patients undergoing cingulotomy (41, 42). Taken together, these studies represent further evidence for the involvement of a central pathway encompassing the ACC and vlPFC in DBS for OCD beyond structural connectomics. Still, they also show that further circuitries, especially involving the vmPFC, are likely to be affected by DBS for OCD. In summary, connectomic studies for OCD-DBS provide growing evidence that a specific pathway within the ALIC carries out reductions in obsessions and compulsions, which is in parts supported by studies using different modalities (fMRI, PET, Electrophysiology). As outlined below, studies using different stimulation sites (ALIC, NAc, STN) are for the most part congruent in that modulation of fibers from the medial and lateral PFC, centrally traversing the ALIC and connecting the STN and thalamus, accounts for positive outcomes of OCD-DBS.

Anatomical considerations

While some of the aforementioned studies agree on the critical role of the same fiber bundle published as a three-dimensional dataset (11, 12, 31–33, 36), others revealed *seeming* heterogeneity about which pathway would be critical to modulate for successful DBS in OCD. Namely, the study by Liebrand et al. suggested that the MFB, connecting the PFC with the ventral tegmental area, would be associated with a beneficial response (28) whereas other studies highlighted streamlines within the ALIC as being critical for OCD-DBS (11, 32, 44). Conventionally, the MFB is a transhypothalamic structure that does not traverse the ALIC (20, 21) – and seen in this light, the studies would imply a conflicting finding. Reviewing the respective literature more in depth, however, suggests that this apparent discrepancy is in fact a matter of nomenclature. The fiber tract defined by Liebrand et al. (28) labeled as MFB was reconstructed using dMRI by placing a seed to the ventral tegmental area and a waypoint seed *into the ventral ALIC*. This resulted in a bundle that passed the ALIC considerably dorsally to the NAc (figure 4; while the ATR was largely running more ventrally in the original publication). The group was relying on former work by Coenen et al. who conceptualized the tract based on dMRI tractography (referred to as superolateral branch of the medial forebrain bundle, slMFB) as a potential target for treating depression (34, 45). However, anatomy textbooks of the human brain (46), histological atlases (47, 48) and a recent anatomical review of brain regions relevant for OCD-DBS (21) confirms that the MFB is *not part* of the internal capsule (Figure 4). Thus, the streamlines referred to as slMFB instead represent fibers of the internal capsule. Of note, there is uncertainty whether it is the ventral tegmental area that is sending projections through the internal capsule to the PFC or descending PFC-brainstem connections that send axon collaterals to regions such as the STN and ventral tegmental area (21). Thus, a more appropriate description of the pathway described by Liebrand et al. may indeed be a cortico-midbrain projection traversing within the ALIC. These insights harmonize aforementioned findings with reports of the slMFB/midbrain target/VTApp as an effective target for OCD (24) which, by its shape, again represents the same bundle (49).

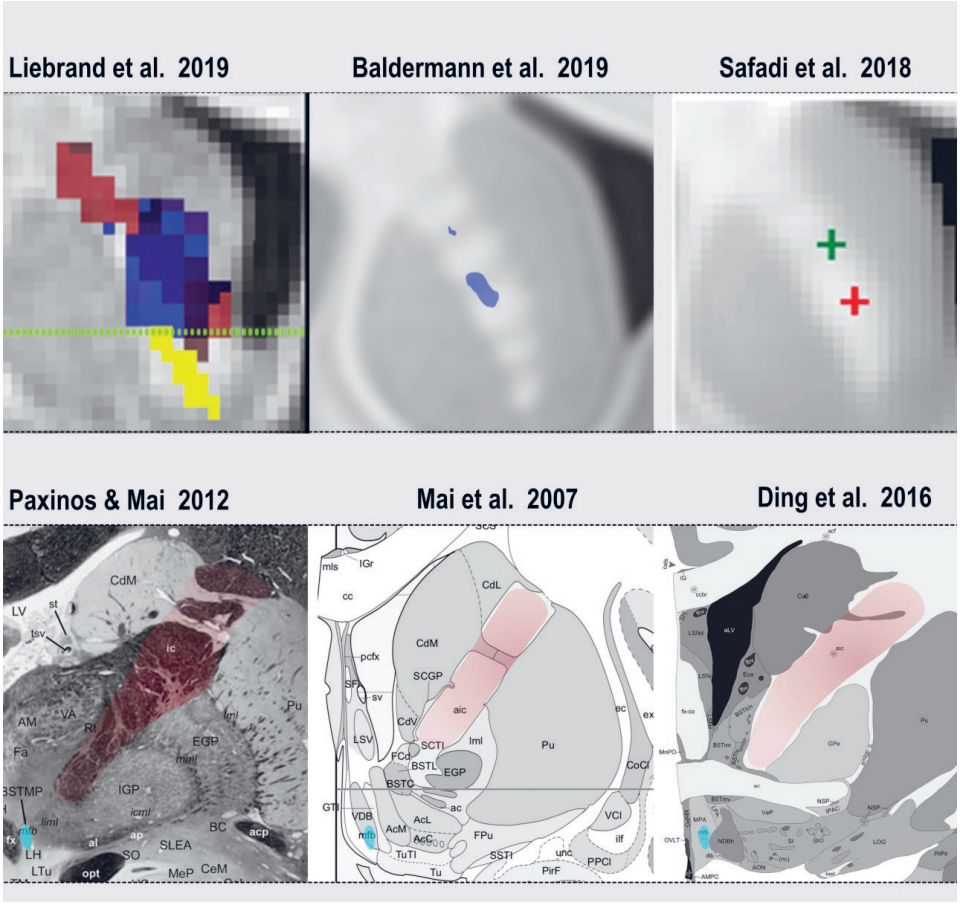


Figure 4: Differences in anatomical nomenclature have led to confusion in the deep brain stimulation for obsessive compulsive disorder literature. Top: Optimal tract targets mediating DBS treatment by Liebrand et al. (39) and Baldermann et al. (42) are marked in blue. The former was termed medial forebrain bundle (MFB) while the latter was termed frontothalamic radiation / anterior limb of internal capsule (ALIC). Based on anatomical tracer data in macaques (62), this site within the central ALIC best conforms to projections from the dorsal anterior cingulate cortex (dACC) and ventrolateral prefrontal cortex (vlPFC) (right). Bottom: classical definition of the MFB (cyan) in coronal sections from three anatomical reference atlases (59; 60; 64) compared to the ALIC (red). According to these atlases, the MFB takes a transhypothalamic route and is not part of the ALIC. Panels by Liebrand; Paxinos & Mai; Mai reproduced, with permissions from the original publication. Panel by Safadi et al. reproduced under the Creative Commons Attribution 4.0 International License (CC-BY). Panel from Ding et al. retrieved from https://www.brain-map.org.

Assembling all evidence, multiple studies from differing research groups, differing patient samples and targets converge on a highly similar optimal stimulation site within the ALIC (Figure 5) – although authors had used different pathophysiological concepts to explain results (Figure 1, 4). Evidence from non-human primate tract tracing suggests that this spot may best be described by the central portion of the ALIC connecting to dACC and vlPFC (21, 50). The hyperdirect pathway projecting from dACC to STN was the most predictive tract from a set of anatomically predefined pathways in the N = 50 study by Li et al. (12). In a recent report, the same N = 50 patients studied by Li et al. were reexamined based on functional connectivity, which has the advantage to include indirect connections. Again, a common network attributed a strong role to the dACC (10). Further support for the dACC as a strong cortical candidate region is provided by the efficacy of anterior cingulotomies in treating OCD (figure 2) (51). Furthermore, an FDA approved H-coil transcranial magnetic stimulation (TMS) system targets the dACC and medial prefrontal cortex (52). Other DBS studies have also reported the importance of the vlPFC (12, 31) and middle frontal gyrus (MFG)/dlPFC (11, 27). As shown in figure 3 (data based on (21, 50)), white matter tracts from the PFC/ACC travel through the ALIC in a topologically organized manner at this specific central part of the ALIC. By nature, dMRI based tractography may not be able to distinguish these cortical representations with certainty. Moreover, as outlined above, the optimal network is probably not limited to this specific pathway and further networks attributable to differential symptoms have been described (7, 35) (also see Figure 7 for a specific example). Subcortically, the connectomic evidence so far highlights the pivotal role of the amSTN and the thalamus (12).

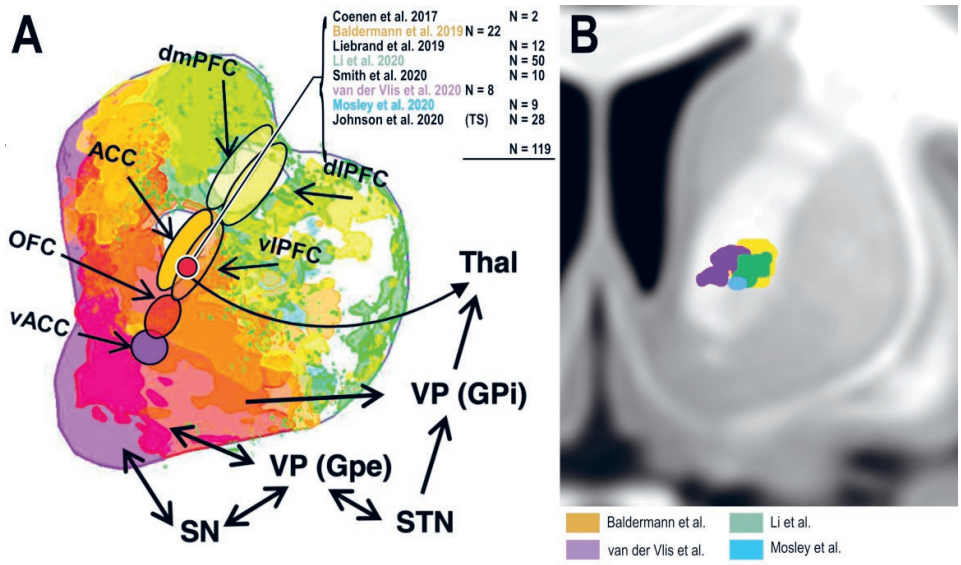


Figure 5: Synopsis of anatomical organization of the ALIC with tractography results of OCD-DBS studies. A) Anatomical organization of the anterior limb of the internal capsule (ALIC) as reported by Haber et al. 2020 (17). A central part of the ALIC has been used by most if not all studies investigating the matter (see list). Note that the N = 22 patients from Baldermann et al. were used in Li et al., as well, hence were only counted once when calculating the sum of 119 patients across studies. Note that the cohort reported by Johnson et al. (55) comprised Tourette Syndrome patients with comorbid obsessive-compulsive symptoms. Figure adapted, with permission, from Haber et al. 2020 (17). B) Synopsis of studies from Baldermann et al., Li et al., van der Vlis et al. and Mosley et al. that converge on a similar region. dmPFC = dorsomedial prefrontal cortex; dlPFC = dorsolateral prefrontal cortex; ACC = anterior cingulate cortex; vlPFC = ventrolateral prefrontal cortex; OFC = orbitofrontal cortex; vACC = ventral anterior cingulate cortex; SN = substantia nigra; VP = ventral pallidum; Gpe = globus pallidus externus; STN = subthalamic nucleus; GPi = globus pallidus internus; Thal = thalamus.

A mechanistic model of connectomic neuromodulation for OCD

Based on the evidence of connectomic DBS for OCD reviewed above, we propose a novel network model for an underlying mechanism of neuromodulation for OCD. Data so far indicates that modulation of a hyperdirect connection of medial and lateral prefrontal cortices to the STN is associated with DBS response. Thus, the STN as an entry point for cortical information in terms of a hyperdirect pathway appears to be highly relevant for treatment of OCD, apart from the commonly accepted dysfunctional frontostriatal input

related to the direct and indirect pathway (53, 54). Secondly, projections between the anterior thalamus and PFC seem important (figure 6). Considering the topological configuration of white matter tracts in the ALIC, the pathway can be described as a *central* ALIC pathway. Precise origination and termination points of this pathway remain unclear. However, some clues exist. As outlined, the dACC is a strong candidate derived from tractographic studies and is in line with alternative effective neuromodulation strategies for OCD, i.e., cingulotomy and TMS. However, methodological limitations prevent a definite conclusion regarding other cortical areas (i.e. vlPFC, dlPFC and vmPFC) that may be involved (table 1).

Crucially, modulation of this circuit could take place at different nodes of the network: First, via DBS to the ALIC, STN, thalamus, and, potentially, GPi. Second, via ablative neurosurgery to dACC and ALIC and third, via transcranial magnetic stimulation of the dACC. Importantly, the different targets within this loop are not necessarily interchangeable. Indeed, the fact that different targets are equally capable of modulating this specific network makes it even more important to understand which surmounting *difference*s exist between them. For instance, a clinical trial including both the ALIC/NAc and the STN target in the same patients revealed different structural connectivity of these targets, although clinical improvement of obsessive-compulsive symptoms of both targets could be assigned to the same pathway (35). This suggests that each target *additionally* modulates different brain networks and, possibly, functions. Indeed, the authors distinguished that while ALIC/NAc-DBS had a greater effect on comorbid depression, STN-DBS was associated with improved cognitive flexibility. Considering the high prevalence of comorbidities in OCD patients (55), such specific symptom profiles may be of great use in the future to offer patients a tailored intervention deliberately responding to their symptom profiles.

Finally, although evidence from available studies remains scarce, the concept of a common network for improving OCD symptoms may be independent of the disorder. As outlined, comorbid obsessions and compulsions in patients suffering from Tourette Syndrome improved when the central ALIC pathway was stimulated (36) (figure 3). Thus, the proposed network may be effective in improving obsessions and compulsions, rather than OCD (as a categorical disease). Importantly, OCD is a highly heterogeneous disorder. Apart from specific OCD subtypes, e.g., washing, checking, etc., the putative underlying neuro-psychological mechanisms are also widespread, e.g., impaired habit vs. goal-directed behavior, cognitive inflexibility, emotional vulnerability or altered risk evaluation. These underpinning principles may in turn serve as transdiagnostic dimensions for other compulsivity-related disorders, such as behavioral addiction, substance use disorders, Tourette Syndrome and autism-related stereotypies (53, 56). Thus, a next step for a more effective and personalized neuromodulation for OCD will be to characterize these endophenotypes and identify through which networks each may be effectively modulated (7).

This framework adds important insights to the prevailing network models for OCD. Based on ground-breaking animal studies that proved the critical role of the OFC for compulsive

symptoms (57, 58), researchers have often focused on the role of orbitofronto-striatal dysfunctions to explain clinical effects of DBS (59). To date, we understand OCD as a multiple circuit disorder where each pathway contributes to different aspects of the disease (7, 54, 60). In line with this notion, connectomic studies for OCD DBS provide evidence that modulation of specific circuits relevant in OCD pathophysiology (i.e. a central ACC-ALIC-STN pathway and possibly a vmPFC-related pathway) can lead to clinical improvement. Further, our review highlights the potential role of the STN in OCD therapy as an entry point for cortical information from the PFC in terms of a hyperdirect pathway.

Further pathways and factors relevant for neuromodulation for OCD

We must reiterate that this *proposed* mechanistic model forms *one* possible mechanism of action – and could represent part of a larger network. Modulation of additional loops (e.g. ventral and dorsal frontostriatal loops, fronto-midbrain connections) and respective changes in symptom dimensions will further contribute to specific therapeutic outcomes (7). This is reflected by the fact that although a common pathway could be derived from connectomic studies in OCD DBS, there are evidently subjects that did not modulate this pathway but still profited from DBS (12, 32, 36), implying that additional circuits will be relevant to consider. As an example, DBS for OCD is capable of modulating affective states (i.e. anxiety, mood) associated with changes of activity in a network comprising the vmPFC, insula and amygdala (8). This is in line with changes in depression scores linked to modulation of a more ventrally located loop within the ALIC (figure 7B) (11). Congruent to this, it was recently shown that transcranial alternating current stimulation of the OFC improved obsessive-compulsive behavior in a cohort of healthy subjects by interfering with reward-related beta-gamma oscillations (61) (Figure 7). Given that antidepressant effects of DBS are likely to result from modulation of fronto-striatal fibers (81), the fronto-striatal input may also play a decisive role for improving affective states in OCD. The importance of this circuit for OCD DBS is also supported by animal studies, showing that optogenetic stimulation of the OFC-VS pathway decreases grooming in a rodent model of OCD (75). A later study in the same OCD mouse model revealed that both DBS of the VS and ALIC resulted in a significant reduction in grooming independently (though the ALIC target was more effective on average), suggesting that both pathways are contributing to therapeutic success (82). Further evidence supporting the involvement of an affect-related circuitry stems from the comprehensively discussed study by Mosley et al., where connectivity with the amygdala was also associated with DBS response, along modulation of the central ALIC (83). Importantly, these different therapeutic circuitries may correspond to improvement of different symptom or neuropsychological dimensions of OCD. Thus, we emphasize that in the same manner as different basal-ganglia cortical loops are implicated in the pathophysiology of OCD (7), neuromodulation of different circuits may contribute to therapeutic success.

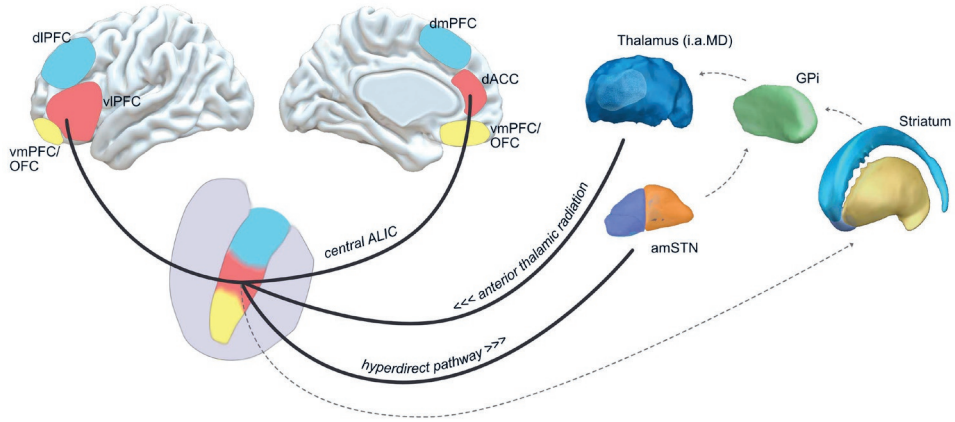


Figure 6: A proposed mechanism of action for connectomic neuromodulation in obsessive-compulsive disorder (OCD). Displayed are areas implicated in the pathophysiology of OCD (upper right) and their representation within the anterior limb of the internal capsule (ALIC) (bottom left). The right panel schematically illustrates connections with the basal ganglia. Solid arrows represent evidence from connectomic studies so far: effective DBS is associated with fibers from the medial (dACC) and lateral prefrontal cortex (vlPFC) that travers the ALIC centrally. Subcortically, these fibers connect with the anteromedial part of the subthalamic nucleus (amSTN), representing a hyperdirect pathway. Additionally, modulating fibers from the Thalamus (inter alia the medial dorsal nucleus, MD) to the PFC along the ALIC (not illustrated) seem to contribute to clinical outcome. Additional loops that may contribute to beneficial effects of DBS for OCD include a ventral loop from the ventromedial and orbitofrontal cortex (vmPFC/OFC), connecting with the ventral striatum and a dorsal loop involving the dorsolateral (dlPFC) and –medial prefrontal cortex (dMPFC).

Table 1: Structural connectomic studies of DBS for obsessive-compulsive symptoms

Study	N	Indication	Target	Connectivity estimate
Hartmann et al. 2016	6	OCD	ALIC/NAc	Normative structural connectivity
Baldermann et al. 2019	22	OCD	ALIC/NAc	Individual and normative structural connectivity
Liebrand et al. 2019	12	OCD	ALIC/NAc	Individual structural connectivity
Li et al. 2020	50	OCD	ALIC/NAc, STN	Normative structural connectivity
Mosley et al. 2020	9	OCD	BNST	Normative structural connectivity
Smith et al. 2020	10	OCD	ALIC/Nac	Normative structural connectivity
Johnson et al. 2020	28	GTS	GPi	Normative structural connectivity
Van der Vlis et al. 2020	8	OCD	VC/VS	Normative structural connectivity

OCD = Obsessive-Compulsive Disorder; GTS = Gilles de la Tourette Syndrome; ALIC = Anterior limb of internal capsule; Nac = Nucleus accumbens; STN = Subthalamic nucleus; BNST = Bed nucleus of stria terminalis; VC/VS = Ventral capsule/Ventral Striatum; MFG = Middle frontal gyrus; DLPC = dorsolateral prefrontal cortex; PFC = prefrontal cortex; dACC = dorsal anterior cingulate cortex; vlPFC = ventrolateral prefrontal cortex; am = anteromedial; FTR = frontothalamic radiation; VTA ventral tegmental area; pp = projection pathway

Although several randomized controlled trials (23, 31, 62) have shown that DBS is effective in OCD, meta-analytic response rates of 60 % (95 % CI = 49-39) are still lower compared to DBS for movement disorders such as Parkinson's disease or Essential Tremor (63). So far, there is insufficient knowledge about reliable response predictors. Larger volumes of the striatum seem to be associated with better outcomes (64) and a meta-analysis identified an association between age at OCD onset and presence of sexual/religious obsessions and compulsions with beneficial outcomes (63), but effect sizes were small and other clinical

Methodology	Beneficial connectivity		
	Cortical representation	**Subcortical representation**	**Pathway specification**
Pathway-activation models	Right MFG/dlPFC		ALIC
DBS network modeling, Fiber filtering	Medial and lateral PFC	Thalamus, Nucleus subthalamicus, BNST	FTR /ALIC
Spatial pathway dependency	PFC	ventral tegmental area	VTApp/Midbrain pp
Fiber filtering	dACC, vlPFC	amSTN, MD	ALIC
DBS network modeling, Fiber filtering	Right vlPFC	BNST, Amygdala, circuit of Papez	ALIC
Fiber filtering	Validation of the pathway identified in Li et al. 2020		
Pathway-activation models	Associative/sensorimotor pallido-subthalamic pathway and internal capsule Validation of the pathway identified in Li et al. 2020;		
Fiber filtering	Medial and lateral PFC	STN	ALIC
	Validation of the pathway identified in Li et al. 2020		

trials found no differences between outcomes across symptom dimensions (65). There is also uncertainty about optimal stimulation parameters (e.g. frequency, pulse width) for OCD, as systematic comparative studies hereof are lacking (66).

Clinical trials of the ALIC/NAc/BNST region typically use high amplitudes (e.g. ranging from 3-7 Volt (65), 3.5 – 5 Volt (62) or targeted at 4.5 Volt (31)), while effective STN DBS required lower amplitudes (e.g. ranging from 1-4 Volt (67)). In all of these trials, a monopolar high-frequency stimulation (> 80 Hz) was applied, the pulse width was mostly selected above 60 µs, although often considerably higher (up to 120-450 µs) for the ALIC/NAc/BNST area (65, 68). For the previously discussed studies on connectomic DBS for OCD, no specific patient selection and similar stimulation parameters were chosen (31–33, 35, 65). Higher activation thresholds of fibers of passage (e.g. in the ALIC) over axons terminating in a nucleus (e.g. in the STN) may have led to differences in stimulation amplitudes and pulse widths (69). Furthermore, on average and across centers, ALIC stimulation volume centers were more

distant to the central ALIC target than in the STN groups – which could again explain lower stimulation amplitudes applied in the STN target.
Following the pioneering example of connectomic DBS for depression (70, 71), prospective studies are now necessary to validate observations in DBS for OCD to make a step towards a more tailored, precise and thus safe and effective neuromodulation for OCD.

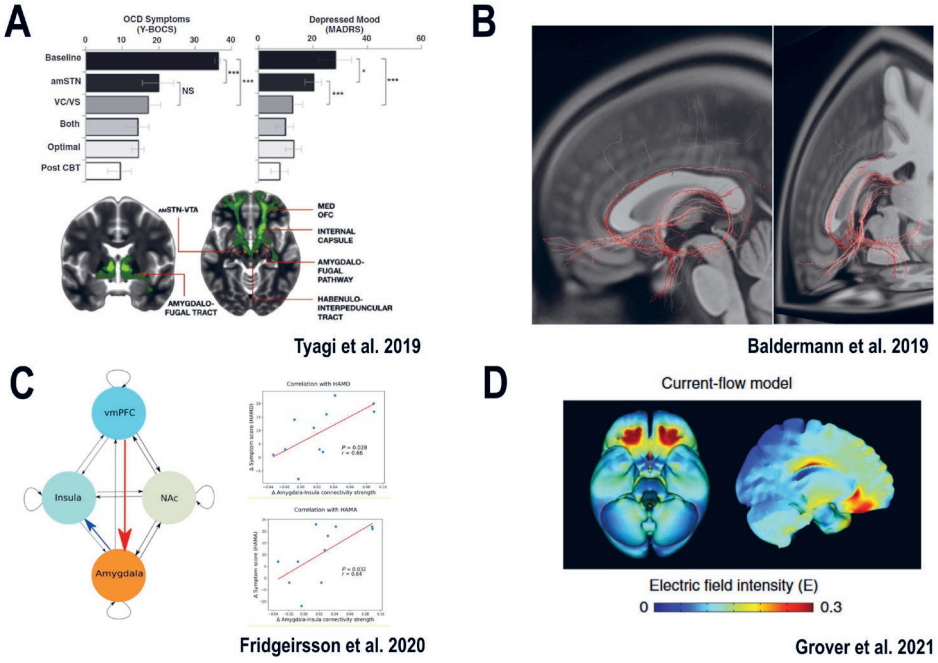


Figure 7: Evidence for a ventral reward/affect-related loop relevant for deep brain stimulation (DBS) in obsessive-compulsive disorder (OCD). A: A randomized controlled trial (54) targeting the anteromedial subthalamic nucleus (amSTN) and ventral capsule/ventral striatum target showed that the latter was more effective in reducing comorbid depression, while both target showed similar efficacy on OCD symptoms. B: A supplementary tractographic analysis by Baldermann et al. (42) showed that reductions in depressive symptoms after DBS of the anterior limb of internal capsule (ALIC) were associated with more ventrally located fibers connecting the ventromedial prefrontal cortex (vmPFC) and the subgenual cingulate cortex. C: Fridgeirsson et al. (56) revealed that switching (ALIC) stimulation off resulted in a dramatic increase in anxiety and depression, accompanied by changes in a functional network involving the vmPFC, amygdala, insula and nucleus accumbens D Grover et al. (71) demonstrated that cortical stimulation of the orbitofrontal cortex/vmPFC with transcranial alternating current resulted in a decrease of obsessive-compulsive symptoms in healthy adults, mediated by a reward related network. All panels reproduced, with permission, from original work as indicated. Panel A reproduced from Tyagi et al. 2019 under the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0).

Limitations and Methodological considerations

Connectomic DBS for OCD is a novel and emerging field that comes in hand with relevant limitations. Primarily, the most studies have relied on small cohorts (inherent to psychiatric DBS), which comes with a greater risk of false positive findings. Second, connectomic studies for DBS strongly depend on the validity of the modelled white matter pathways and how activation hereof is determined which is again subject to relevant limitations. In case of OCD, many studies relied on a similar whole-brain normative connectome and fiber filtering approach based on isotropic electric field models (11, 31–33, 36). More complex biophysical field modeling methods have been developed that may lead to more detailed insights and superior results when predicting clinical effects, in the future (69, 72, 73). For a discussion on potential limitations of activation volume tractography (as performed in most OCD-DBS studies, so far, vs. tractography activation models (as performed for instance in the study by Hartman et al. (27), or pathway activation models, we refer to the excellent publication by Gunalan et al. (26). Third, until now, there is no prospective validation of the identified pathways in OCD DBS. Prospective tractography-based DBS however can result in substantial differences across centers, putatively due to differences in tractographic analysis (74). Despite these limitations, the field of connectomic DBS for OCD has made tremendous progress in the past years and the current evidence stems from multiple centers using different targets and has been partly cross-validated using different connectivity estimates (e.g. dMRI and histology-based atlases).

Conclusion

In summary, we review evidence for a unified network spanning between cortical (dACC, vlPFC and assumingly others) and subcortical (anteromedial STN, MD nucleus of the thalamus) regions that – when modulated by means of DBS, ablative surgery, or noninvasive neuromodulation – alleviates obsessive-compulsive symptoms. We critically review studies that seem conflicting given different uses of nomenclature and conclude that there is instead high concordance between them – especially regarding a specific surgical target site within the ALIC. Finally, we provide a mechanistic model with the most salient addition to include a limbic/associative hyperdirect pathway that traverses within the central segment of the ALIC as a critical component for clinical efficacy.

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Disclosures

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Chapter 4

Network analysis in gamma knife capsulotomy for intractable obsessive-compulsive disorder

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Abstract

Introduction

Gamma-knife Ventral Capsulotomy (GVC) targeting fiber tracts connecting the prefrontal cortex and subcortical structures has been suggested as an efficacious treatment for a subset of patients with treatment refractory obsessive compulsive disorder (OCD).

Research question

The goal of this study was to investigate neural correlates of GVC and investigate the predictive value of white matter tracts that are known to be associated with clinical outcome to Deep Brain Stimulation (DBS).

Material and Methods

MR images of 8 treatment-refractory OCD patients with a minimum follow-up of 3-years who underwent GVC were used to correlate lesion characteristics with symptom improvement. This exploratory study investigated relations between differences in cortical grey matter structure and subcortical stuctures before and after GVC for responding and non-responding patients (n=6). Normative diffusion MRI- based tractography was used to determine networks associated with successful lesions.

Results

The mean total Y-BOCS reduction was 19.6 after three years, resulting in a response rate of 63%. The strongest correlation with symptom improvement was found for a decrease of the left ventral diencephalon volume ($r=-0.83$, $p=0.039$). Discriminative tractography suggest streamlines connecting the prefrontal cortex with the subthalamic nucleus to be associated with clinical response. However, results could not be validated either implicating interpatient anatomical variability or reflecting the relative small sample size as a limitation.

Discussion/Conclusion

Taken together, the present study highlights the efficacy of GVC in patients with treatment-refractory OCD. Our results are suggestive of GVC treatment efficacy being mediated by the involvement of a subpart of the ALIC connecting the PFC and the STN.

Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurrent, unwanted, and disturbing obsessions (thoughts, urges or images) and/or repetitive behaviors/mental acts (compulsions) aimed at reducing or preventing anxiety or distress. OCD has an estimated lifetime prevalence of 1.6% and is associated with a higher risk of suicide, an increased risk of metabolic and cardiovascular disorders and increased rates of long-term labor-market marginalization.[1–4] Most patients will experience some symptom relief after receiving cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) either alone or in combination.[5] However, an estimated proportion of 40-60% responds insufficiently to treatment, prompting the investigation of alternative treatment augmentation strategies, i.e. switching to a different SSRI or clomipramine, addition of neuroleptic agents and ultimately, neuromodulation therapies or ablative surgery.[5]
Neurosurgical techniques, focused on lesioning or modulating components of the neural circuitry implicated in OCD, have been used for decades in the treatment of adults with severe, treatment-refractory symptoms. Neurobiological models posit that dysfunction of corticostriatal-basal ganglia-cortical circuits (CBGCs) connecting orbitofrontal cortex, anterior cingulate, basal ganglia, and thalamus underlie OCD pathophysiology as evidenced in neuroimaging studies.[6,7] Four main ablative procedures have emerged for treatment-refractory OCD: anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy and limbic leucotomy (a combination of anterior cingulotomy and subcaudate tractotomy).[8,9] Among these ablative procedures, anterior capsulotomy has been associated with the highest response rate.[8] Contemporary techniques for anterior capsulotomy include Gamma Knife radiosurgery (GKRS), magnetic resonance-guided ultrasonography (MRgFUS and laser interstitial thermal therapy (LITT).[8,10,11] Deep Brain Stimulation (DBS), a nonablative and adjustable procedure was introduced in 1999 as an alternative treatment to ablative surgery for treatment-refractory OCD.[12] The effectiveness of DBS, aimed at different target structures for OCD, has subsequently been established by several placebo controlled randomized controlled trials.[13–16] A recent meta-analysis showed an equal efficacy of ablative surgery compared to DBS.[17] However, for DBS of the nucleus accumbens (NA) a higher rate of mild and transient impulsivity has been reported.[17] A significant body of literature demonstrates that electrical stimulation is able to suppress abnormal activity in frontolimbic circuits associated with OCD, thereby associating specific white matter tracts with clinical response, *figure 1*.[18–21] Similar functional and anatomical analyses for Gamma Knife anterior capsulotomy remain scarce.[10]

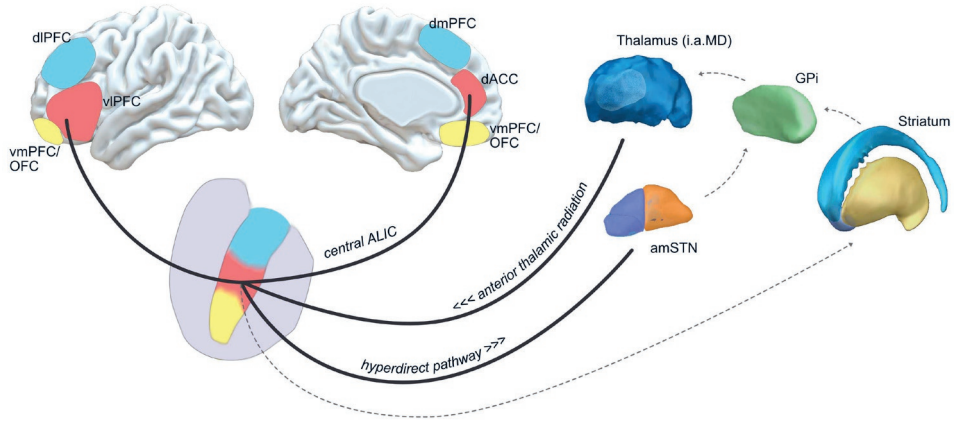

Figure 1. A proposed mechanism of action for ALIC DBS, hypothesized to be involved in GVC. Displayed are areas implicated in the pathophysiology of obsessive-compulsive disorder (upper right) and their representation within the anterior limb of the internal capsule (ALIC) (bottom left). The right panel schematically illustrates connections with the basal ganglia. The central ALIC serves as a hub for various pathways associated with OCD; the vlPFC to dACC and STN pathways as well as the thalamus to vlPFC pathway. Abbreviations; dACC: dorsal anterior cingulate cortex; vlPFC ventrolateral prefrontal cortex; amSTN: anteromedial subthalamic nucleus; MD thalamus: medial dorsal nucleus of the thalamus; vmPFC ventro-medial PFC; OFC: orbitofrontal cortex; dmPFC: dorsomedial prefrontal cortex; GPi: globus pallidus internus.

This study aims to contribute to the anatomical understanding of anterior capsulotomy by morphometric analyses and incorporating recent connectomic findings in DBS-OCD literature into imaging data of 8 treatment-refractory OCD patients treated with GKRS.

Methods

Patients/ Gamma Ventral Capsulotomy procedure

In this retrospective cohort, 8 patients were selected for Gamma Knife Ventral Capsulotomy (GVC) between the period of 2011 – 2016 according to the inclusion criteria as previously described.[22] These patients were from a previously described cohort of treatment refractory OCD patient treated with GVC and selected based on the availability of post-GVC MRI data. [22] These criteria included the diagnosis of severe OCD on the basis of DSM-IV, with a Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score of at least 25. This level of impairment should have persisted for a minimum of 5 years, despite adequate trials or intolerance to two selective serotonin reuptake inhibitors and clomipramine, augmentation strategies (i.e., antipsychotic medications), and CBT. Patients with a reduction in Y-BOCS scores of 35% or more were considered responders.
GKRS was performed using Leksell Gamma Knife® model 4C (2009–2012) or Perfexion™ (2012–2016). A Leksell stereotactic frame (Elekta Instrument, Stockholm, Sweden) was mounted on the skull under local anesthesia, and a peri-operative contrast enhanced MRI-scan of the head with frame was acquired. Treatment plans were performed using the GammaPlan Software (Elekta Instruments, Stockholm, Sweden). The bilateral target was the most ventral margin in the center of the ALIC. The targets were irradiated by a maximum dose of 140-150 Gy with 1 or 2 shots using 4-mm collimators.[22] For a more detailed description of GVC procedures, we refer to earlier papers.[22,23]

Imaging, GVC-lesion segmentation and normalization

All subjects had a 3-T MRI 1 year after GVC (Siemens, Erlangen, Germany). The sequence used was a 3DT1 (voxel size 1x1x1mm) with gadolinium. GVC volumes were segmented on T1 sequences in ITK-SNAP V.3.8.0 (itksnap.org) as the contrast-enhancing volume including the hypointense center.[24] Pre-GVC MR-images were normalized into ICBM 2009b Non-linear Asymmetric ("MNI") template space using the SyN approach implemented in Advances Normalization Tools (ANTs), with an additional subcortical refinement stage as provided in the Lead-DBS pipeline.[25–27] GVC volumes were then normalized into ICBM 2009b Non-linear Asymmetric ("MNI") template space using SPM12 (fil.ion.ucl.ac.uk/spm) as provided in Lead-DBS. In the absence of Pre-GVC MR-images (n=2), GVC volumes were normalized into MNI template space as implemented in LESYMAP, a package available in R.[28] Ablation volumes were averaged to create heat maps and subsequently binarized for normative tractography analysis.[10,29] Heatmaps were visualized in FSLeyes 5.0.10.[30]

Morphometry

All available pre-post GVC MR-images (n=6) were processed using Freesurfer image analyses suite version 7.2, which automatically reconstructs a three-dimensional model of the cortical surface for cortical thickness measurement and provides a mean thickness and volume within automatically defined cortical parcellations and subcortical segmentations in each hemisphere and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications.[31–33] Minor adjustments to the automated segmentation and parcellation routines were made when necessary (e.g. adding control points to facilitate grey/white matter classification), but no major alterations were necessary. The left and right hemispheres were registered to the fsaverage atlas (common surface space) templates included in FreeSurfer, and smoothed with a Gaussian kernel of FWHM 10 mm.

Separate General Linear Models (GLMs) were constructed to analyze the effect of GVC on cortical volume and thickness (GMV, GMT; pre- vs. post-GVC) and correlation with OCD symptom reduction. All vertex-wise results were thresholded at an individual vertex level of $p < 0.001$, and cluster extent thresholds corrected for multiple comparisons with a 5% (FDR) were calculated through Monte Carlo simulations of white noise on the cortical surface. The model included Y-BOCS reduction and patient age. We did not include Total Intracranial Volume (TIV) in the model as a covariate in the GLMs, as we were specifically concerned with modelling correlations with individual differences in GMV and GMT. For subcortical structure analyses, we included 10 subcortical structures for each hemisphere. The subcortical volumes were not corrected for TIV. Individual Y-BOCS reduction was correlated with the difference of pre- and post-GVC subcortical structure volumes.

Normative tractography

In order to identify discriminating fiber bundles associated with clinical response to GVC, we adapted the methodology of Li *et al.*[21,34,35] Accordingly, based on a normative connectome, individual fibers were assigned a 'Fiber T-score' by correlating the fiber tract's connectivity to GVC volumes across patients with clinical outcome.[36,37] Validation of the tracts was sought by performing a k-fold cross prediction. Second, connectivity estimates were calculated between the averaged (non-) responder ablation volumes and cortical parcels of the PFC, as provided in Lead DBS. MNI cortical parcels of the PFC were generated by combining Brodmann areas 8, 9, 10, 46 (dorsolateral PFC); 44, 45, 47 (ventrolateral PFC), and 12, 25, 32, 33, 34 (ventromedial PFC) as provided in the Brodmann Atlas of the WFU PickAtlas v2.4 in SPM12.[38]

Gamma Ventral Capsulotomy vs. Deep brain stimulation for intractable obsessive-compulsive disorder

To provide for a direct anatomical comparison between GVC lesion volumes and DBS Volume of Tissue Activation (VTA), we combined data of 8 previously described OCD patients receiving ventral capsule/ ventral striatum VC/VS stimulation.[34] The Euclidean distance between 'hottest' voxel of the averaged GVC volumes and VTAs was calculated using MATLAB (R2020a, Mathworks, Natick, Massachusetts). Recent connectomic findings in DBS for OCD, have identified a connectivity profile positively associated with clinical outcome.[21] Specifically, streamlines connecting dorsal anterior cinculate cortex (dACC), the lateral and medial prefrontal cortex with the anteromedial STN and medial dorsal nucleus of the thalamus were associated with successful DBS.[21] This tractographic profile was made publicly and available within Lead-DBS.[26] In order to identify the positive predictive value of these 'DBS' tracts in GVC we adapted the sum-score methodology as described in Li *et al.,* by calculating how many of the DBS associated fibers passed through the patients' GVC volume. Then, for each patient a fiber score was calculated: a sum-score weighted by the t-value of each tract passing through each GVC. As GVC volumes were asymmetrical, we analyzed the left and right hemispheres separately.

Statistical analyses

Clinical outcome variables, fiber count estimates and GVC volumes were compared between non-responders and responders using Mann-Whitney U test. GVC-atlas intersection volumes and (sub)-cortical structure volumes were correlated with treatment outcome using Spearman's correlation and Bonferroni corrected. The Kolmogorov-Smirnov was used to test for normality. P-values<0.05 were considered statistically significant. Unless otherwise indicated, results will be displayed as a mean ± SD. All statistical analyses were performed using IBM SPSS Statistics, version 20 (IBM Corp., Armonk, N.Y., USA).

Results

Patient characteristics

We included 8 treatment-refractory OCD patients with a minimum follow-up of 3-years after with GVC. The mean age of the participants was 35 ± 7.5 years. For a detailed disease and treatment history we refer to our previous publication.[22] The steepest descent in total Y-BOCS scores was observed between 6 months and 1 year -7.1 ± 5.6. Further improvement was observed after one year. At three years follow-up, five patients were considered a responder, while three remained non-responsive, resulting in a response rate of 63%, *figure 2a.* The mean total Y-BOCS reduction was 19.6 after three years, with an equal reduction in YBOCS subscores for obsessions and compulsions. Specified for responders, the mean total YBOCS reduction was 28.8. There were no significant differences in age at surgery, gender or follow-up time at baseline between responders.

Lesion geometry

The mean time between GVC and post-operative imaging was 229 days [89-370 days]. MNI coordinates of the 'hottest' voxels of the averaged lesions of the responding patients were [-20, 18.5, -1.5] for the left hemisphere and [16, 18.5, -1.5] for the right hemisphere, whereas the 'coldest' voxels for non-responding patients was [-17, 16, -8] vs. [15, 16, -4], *figure 3b.* The mean total GVC volume (left plus right) was 326.5 ± 112.9 mm^3, with non-significant larger GVC volumes in the left hemisphere (193.6 ± 165.7 mm^3) when compared to the right hemisphere (112.9 ± 112.9 mm^3), *figure 2c.* No differences were observed for lesion volumes of responders vs. non-responders. Improvement in Y-BOCS was not correlated with left (p=0.867) or right (p=0.469) GVC volume. Volumes of the caudate (left p=0.529, right p=0.763), putamen (left p=0.545, right p=0.736), nucleus accumbens (left p=0.505, right p=0.823), and globus pallidus externus (left p=0.258, right p=0.555) ablated were not correlated with total Y-BOCS reduction, *figure 3a.*

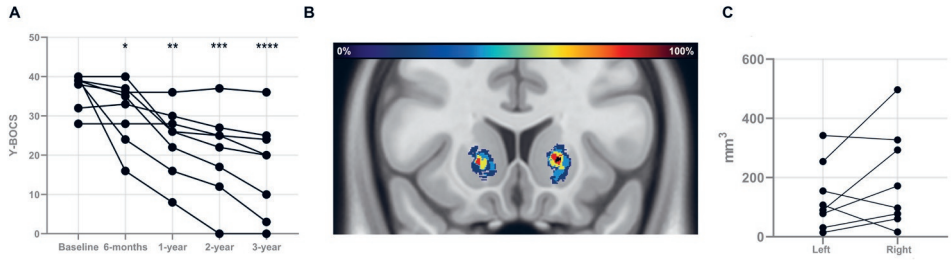

Figure 2. A. Individual Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores for obsessive-compulsive disorder (OCD) patients treated with GVC (A) (*p=0.11; **p=0.014; ***p= 0.011; **** p=0.007). B. Heatmap representing the averaged GVC volumes in ICBM 2009b Non-linear Asymmetric MNI template C. Individual GVC volumes for the left and right hemisphere (C).

Morphometry

Our whole brain analysis revealed no differences of GMV or GMT in both hemispheres following GVC, or correlations between Y-BOCS reduction and cortical structures. Of the 10 ICV corrected subcortical structures in each hemisphere, a negative correlation was found for the left ventral diencephalon, including hypothalamus with mammillary body, subthalamic, lateral geniculate, medial geniculate and red nuclei, substantia nigra, and surrounding white matter (r=-0.83, p=0.039) and the right cerebellum white matter (r=-0.78 p=0.042). There were no differences in pre-GVC subcortical volumes between responders and non-responders.

Connectivity analyses

Fiber T-values to GVC volumes were assigned across patients with clinical outcome as performed in, *Baldermann et al.*[39] Tracts were thresholded to be connected to 20% of GVC volumes. Fiber bundles positively associated with the percentage Y-BOCS reduction originate from the PFC of which a subset to the project to subthalamic nucleus (STN), in accordance with identified tracts associated with DBS response for OCD.[35] Projections traversing through the superior genu of the corpus callosum were negatively associated with GVC response, *figure 3b* However, we were unable to validate the identified tracts in a subsequent prediction analysis using k-fold (K=2) cross validation (r=0.13, p=0.382). There were no differences in fiber count estimates between (non-) responder GVC volumes and the dlPFC, vlPFC or the vmPFC, *figure 3c*.

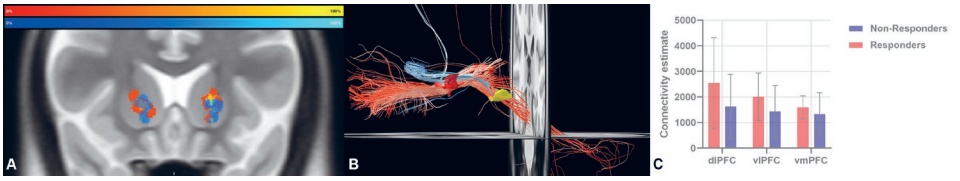

Figure 3. A. Heatmap representing the averaged GVC volumes for responders (red-yellow) and non-responders (blue-light blue) in ICBM 2009b Non-linear Asymmetric MNI template. B. Positive (A) and Negative (B) predicting fibers associated with clinical improvement are shown in red and blue. Dark red: concatenated GVC volumes. Yellow: Subthalamic nucleus. C. Connectivity estimates between GVC volumes of (non-) responders and the dorsolateral, ventrolateral and ventromedial prefrontal cortex.

Gamma Ventral Capsulotomy vs. Deep brain stimulation for intractable obsessive-compulsive disorder

In comparison to the volume of tissue activation of DBS, GVC volumes were located more anterolaterally, with an Euclidean distance of 16.5 and 16.8 between the MNI coordinates of the 'hottest voxels' of averaged VTAs [-8.14, 2.13, -3.91; -17.5, 15.5, 0] and GVC volumes [9.99, 3.23, -3.03; 16; 18.5; -1.5], *figure 4a.* In 4/8 patients GVC ablated bilaterally (a part of) a subtract of the anterior limb of the internal capsule, connecting the prefrontal cortex to the subthalamic nucleus and the mediodorsal nucleus (MD) of the thalamus positively associated with YBOCS reduction, whereas in two patients unilateral involvement of this tract was found. [39] In one patient, GVC volumes did not affect this tract *figure 4b.* We were unable to replicate the association with the previously implicated tracts with clinical response, ($p_{\text{one-tailed}} = 0.786$, *figure 4c*).

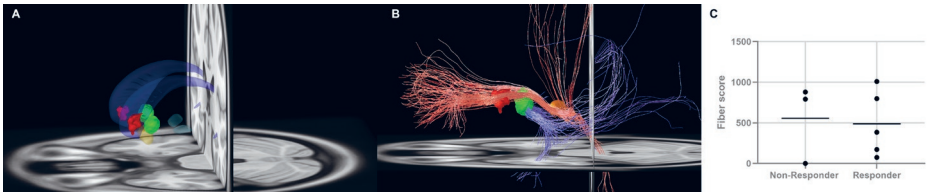

Figure 4. A. Location of GVC volumes (red) in relation to concatenated DBS VTAs (green), caudate nucleus (dark blue), nucleus accumbens (yellow) and subthalamic nucleus (light blue) B. Positive (A) and Negative (B) predicting fibers previously associated with clinical improvement to DBS are shown in red and blue. C. Association between previously implicated white matter fibers and clinical response to OCD DBS.

Discussion

Our analysis of a subset of patients from a previously described cohort of treatment refractory OCD patient treated with GVC supports its clinical effectiveness. The responder rate of 63% and a mean Y-BOCS reduction of 51% after three years of follow up compares favorably with previous reports of GVC for OCD.[17] The current study was unable to support claims that ablative surgery potentially provides immediate relief of OCD symptoms as the maximum response rate was reached after two years of follow-up. [40]

Only a few studies report on lesion volume after ablative surgery for OCD with respect to outcome, where results are contradictory as lesion volume can be positively and negatively associated with outcome.[10,41,42] There is a noteworthy degree of both intra- and inter-modality variability of lesion volumes with a mean total lesion volume following LITT 2400±600mm^3 versus GVC 1737±924mm^3 and lesion volume after MRgFUS lesioning of 362 ± 290 mm^3. Further, hemispherical lesion asymmetry is a common finding following bilateral GVC, as was observed in this case series.[41,42] Recent advances highlight the importance of the anatomical location of the lesion.[10,43] Probabilistic voxel wise efficacy maps of magnetic resonance-guided focused ultrasound MRgFUS treated OCD patients show the region associated with the highest symptom improvement located in the anterodorsal aspect of the ALIC, with an identified region associated with clinical efficacy centred around x = (-)15.5 (±1 mm), y = 10 (±2 mm), z = 4 (±1 m). When compared, GVC lesions associated with symptom improvement in this study were also located in the anterodorsal aspect of the ALIC. However, we were unable to identify an overall difference in Euclidean distance between the 'hottest' voxel of lesions of responders versus non-responders to GVC and the identified MRgFUS sweetspot.[43]

Different regions of the ALIC carry fibers from different prefrontal regions with a ventral–dorsal, medial–lateral, and anterior–posterior organisational topography.[44] Converging evidence from pre-operative DTI and normative connectivity studies identified specific tracts and fibers associated with clinical outcome. Following both ALIC and STN DBS the most clinical effective contacts stimulated thalamocortical ALIC streamlines to the dorsolateral and medial PFC and the rostral anterior cingulate (dACC).[39,45] Furthermore, normative resting-state functional MRI analyses showed that lesion engagement following MRgFUS of the dACC and left dlPFC was correlated with symptom engagement. In our sample, we were not able to replicate the association between ALIC tracts implicated in DBS and clinical response, finding responder and non-responder fiber scores were not different. Further, we were not able to highlight the functional lesional connectivity with the dACC and the dlPFC (data not shown). The inability to replicate both findings could reflect the small sample size as the principal limitation of this study. Using the same methodology our group and others were able to validate and replicate the thalamocortical ALIC streamlines associated with clinical outcome in DBS in relatively small sample sizes (n=8, n=10).[34,46] Implicating that clinical response to OCD-GVC moves beyond a unified connectomic target as response to OCD-GVC was found independent of centroid coordinates and lesion volume in a large cohort of radiofrequency anterior capsulotomy,

suggested to be caused by nontrivial intersubject variability of ALIC fiber organization.[47,48] Moreover, structural predictors of good clinical response to capsulotomy include a decreased gray matter volume of the right inferior frontal gyrus, fiber integrity of the superior longitudinal fasciculus, and lower connectivity of the dorsal caudate with the dACC and an increased streamline counts of the dlPFC – thalamic tracts.[47,49,50]

Our analysis revealed a negative correlation of symptom improvement with the subcortical volume of the left ventral diencephalon including the hypothalamus with mammillary body, subthalamic, lateral geniculate, medial geniculate and red nuclei, substantia nigra and surrounding white matter and right cerebellar white matter. A post-hoc analysis revealed no differences of the volumes of the left ventral diencephalon area or the cerebellum pre-surgery, indicating that variability in response is more likely to be a therapeutic effect. Cerebellar volume alterations were previously shown following thermo-capsulotomy, suggested to be secondary to thalamic atrophy.[51] The structures involved in the ventral diencephalon are part of frontostriatal networks identified to be functionally restored by DBS or GVC.[18,51] Taken together, the left ventral diencephalon might contribute to the effects of GVC.

Taken together, the present study highlights the efficacy of GVC in patients with treatment-refractory OCD. We were not able to identify discriminative fiber tracts associated with GVC clinical response, nor predict clinical outcome using previously identified tracts in DBS, implicating interpatient variability i.e. ALIC fiber organization explanatory for treatment variability. Future research should focus on elucidating neuroanatomical substrates of OCD symptom dimensions and ideally identify the optimal for structural profile relevant to treatment targets for both ablative and invasive neuromodulation for treatment refractory OCD.

Statements

Statement of Ethics
The work described was conducted in accordance with the Declaration of Helsinki. This study was approved by the ethics committee of Koç University (2020.190.IRB1.058). Written informed consent was received from all patients.

Conflict of Interest Statement
The authors declare that they have no conflict of interest.

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Author Contributions
Drs. Bouwens van der Vlis, drs. Samanci designed and conducted the study, data collection, and data analysis. Drs. Peker and drs. Dincer recruited patients and provide the MRI data. Drs. Bouwens van der Vlis prepared the manuscript draft with important intellectual input from Dr. Ackermans, Leentjens, Temel, Samanci and Peker. All the authors approved the final manuscript. The Maastricht University Medical center provided funding for editorial support. Drs. Bouwens van der Vlis, dr. Ackermans and drs. Samanci complete access to the study data.

Data availability statement
Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

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Chapter 5

Cognitive Outcome after Deep Brain Stimulation for Refractory Obsessive-Compulsive Disorder: a systematic review and case series

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Abstract

Introduction

Deep brain stimulation (DBS) is an effective treatment for refractory obsessive-compulsive disorder (OCD). Neuropsychological assessment contributes to DBS treatment in several ways: it monitors the cognitive safety of the treatment, identifies beneficial or detrimental cognitive side-effectsand it could aid to explain for variability, and possibly for treatment -mechanisms.

Background

This systematic review and case-series assessed the cognitive safety and explored explanatory treatment mechanisms of DBS for OCD.

Methods

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.

Results

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.

Conclusion

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.

Key-words: Obsessive Compulsive disorder; Deep Brain Stimulation; Cognitive outcome

Introduction

Obsessive Compulsive Disorder (OCD) is a serious mental health disorder accompanied by a reduced quality of life, particularly in the social, emotional and family domains, and is associated with a significantly increased mortality risk.[1,2] It is estimated that up to 40-60% of OCD patients remain treatment refractory after cognitive behavioral therapy (CBT) and multiple trials with selective serotonin reuptake inhibitors.[3] In the absence of adequate treatment, the course of OCD is often chronic and with a waxing and waning pattern.[4] Deep Brain Stimulation (DBS) has emerged as a safe, well tolerated and effective treatment option for refractory OCD patients with responder rates up to 60%.[5]

Neuropsychological assessment has a fundamental role within DBS treatment and is routinely used for screening potential DBS candidates and evaluating outcome. Neuropsychological assessment contributes to DBS in several ways: it monitors the cognitive safety of the treatment, identifies beneficial or detrimental cognitive side-effects and it could aid to help explaining variability in treatment outcome, and possibly explain treatment mechanisms.[6] In 2012 and 2013 respectively, two systematic reviews concluded that DBS for psychiatric disorders was a cognitively safe procedure. [7,8] However, cognitive deficits have been observed in Parkinson's disease (PD) patients treated with DBS, where it is considered suggested to be the cost for reducing the spectrum of PD motor symptoms (e.g., tremor, bradykinesia, rigidity, and levodopa-induced dyskinesia).[9]

To progress toward a better understanding of cognitive outcome after DBS for OCD, we conducted a systematic review of the literature focusing on studies that report cognitive outcomes across OCD-DBS cohorts, with the intent of performing a meta-analysis. Separate cognitive domains are addressed in dedicated sections. In addition, we present the cognitive outcome of a case series of 7 patients with highly refractory OCD receiving DBS of the ventral striatum/ventral capsule (VC/VS).

Methods

Literature search

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10] The study selection process is summarized in the PRISMA flow diagram (Figure 1).[10] Methods of the analysis and inclusion criteria were specified in advance, documented in a protocol and registered on PROSPERO (International prospective register of systematic reviews, registration number: CRD42020223219).

Search strategy

A comprehensive literature search in the databases EMBASE, PubMed/Medline, Psycinfo and the Cochrane Library was performed based on the search terms "deep brain stimulation" and "obsessive-compulsive disorder" in November 2020 for all studies to date. We refer to supplementary material S1 for the complete search strategy. Reference lists of previously published articles were assessed as an additional source for literature. The search results were restricted to human studies and the English language, no other restrictions were used. We refer to the supplementary S1 for the complete search strategy.

Study selection

Titles and abstracts of all identified studies were screened independently by two reviewers (T.B., M.V.), based on a priori selection criteria. When in doubt of eligibility, the full text of an article was consulted. Discrepancies on in- and exclusions were resolved through discussion and consensus. After primary selection of the articles, full texts of the included articles were assessed by both reviewers and a secondary selection was made based on presence of primary outcome measurements.

Eligibility criteria

Throughout the process of literature selection, clear inclusion and exclusion criteria were followed. We included RCTs, cohort studies, case series and case reports that enrolled OCD patients treated with DBS. Studies not eligible for inclusion were those which had a primary focus other than OCD or did not report the cognitive outcome of OCD-DBS as a single entity and interventions other than DBS. Literature focusing on ethical aspects, (systematic) reviews, letters, animal studies, book chapters and conference abstracts were also excluded. After thorough selection of literature based on title and abstract, the full texts of the included literature were assessed on presence of data on neuropsychological evaluation. Results were analyzed collectively. Primary outcomes were cognitive outcomes, acquired from any type of neuropsychological assessment.

Qualitative assessment

For each included study, qualitative analysis was performed by means of the National Heart, Lung and Blood Institute (NIH) quality assessment tools.[11] Accordingly, studies were therefore categorized on study type. An overall quality score of 'Poor'; 'Fair'; or 'Good' was provided for each study, based on the assessment of the study in each category and number of participants included in the study, *see supplementary material S2*. Due to the low number of included studies, we did not formulate a minimum quality score for inclusion in the analysis.

Data collection

A standardized form was used to extract data from the included studies for assessment of data. The data was extracted by one review author (M.V.) and independently reviewed by a second review author (T.B.). Discrepancies were again resolved through discussion and consensus. To prevent inclusion of same patients several times, due to their inclusion in more than one study or report, we compared patient data between the studies. In the case of cumulative cohorts, only the study with the longest follow-up was included. Unfortunately, it was not possible to conduct a meta-analysis on the cognitive outcome measurements, as there was a heterogeneity in study design, stimulation targets and neuropsychological tests. We prepared a summary for the results on the cognitive outcome and calculated a mean for change in Yale-Brown Obsessive Compulsive Score (Y-BOCS) percentage.

Case series

In addition to the systematic review, we conducted a naturalistic, retrospective study among 7 OCD patients that underwent DBS in our clinic (Table 1). These patients were selected for VC/VS stimulation in the period of 2014 – 2019 according to inclusion criteria based on the criteria proposed by Nuttin et al. and have been described previously.[12] All patients received a standard neuropsychological test battery at baseline and time of follow-up.
This battery contained the Boston Naming Test (BNT) for visual naming and the Rey Auditory Verbal Learning Test (RAVLT) for memory assessment.[13,14] Verbal fluency (VF) was measured by category (animals and occupations) and letter fluency, with the semantic and phonetic verbal fluency tasks respectively.[15] The Stroop Colour-Word Test (SCWT) was used to obtain mental speed and response inhibition.[16] The Trail Making Test (TMT) (part A and B) were used to assess mental speed and cognitive flexibility.[17]
Outcome variables were non-parametrically analyzed using the Wilcoxon signed rank test using IBM SPSS Statistics, version 20 (IBM Corp., Armonk, N.Y., USA). Dichotomous comparison of baseline measures and outcome variables for responders and non- responding and responding patients, with responders defined as patients with ≥35% YBOCS reduction, was performed using the Mann-Whitney U Test. We computed effect sizes according to dividing the obtained Z-score by the root of the number of total pairs ($r = Z / \sqrt{n}$).[18]

Ethical Statement

The work described was conducted in accordance with the Declaration of Helsinki. Approval by the institutional review board and patient consent were not required as the present study has no obligations to the Dutch Act of Scientific Research in Humans.

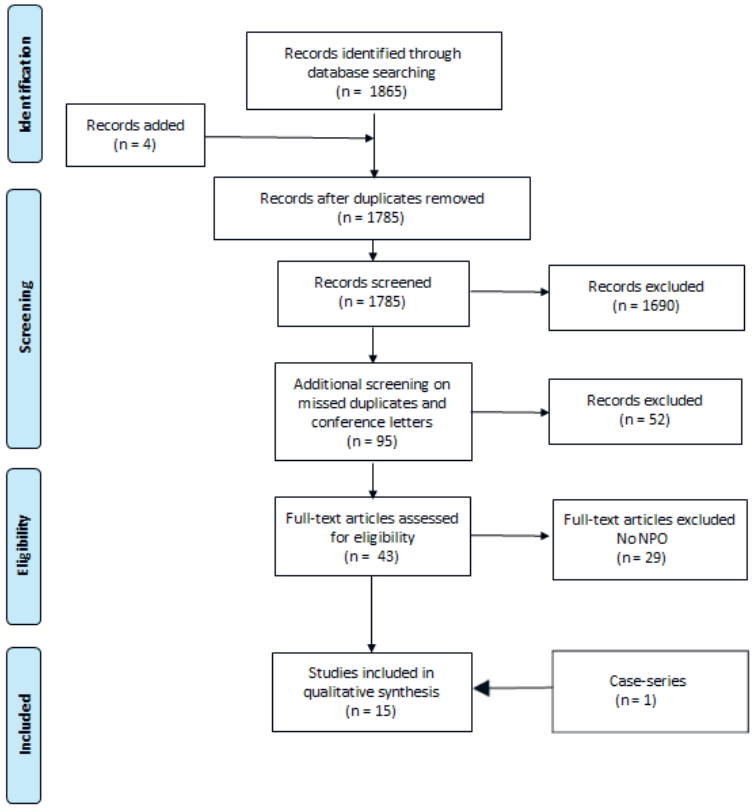

Fig. 1. Prisma flowchart. (Moher et al., 2009)

Results

Search results and characteristics of included studies

In the initial search, 1856 records were identified. After adjustment for duplicates, 1785 records remained, including four studies that were found through cross referencing. Of these, 1690 were discarded because they did not meet our inclusion criteria. After additional screening of these 95 articles and exclusion of conference abstracts, letters to the editor and missed duplicates, 43 papers remained. The full text of these 43 articles were examined and additional 28 studies were excluded, resulting in the final inclusion of 14 studies comprising 171 patients with severe treatment-resistant OCD that underwent DBS (Table 2). Study designs were heterogeneous, including, amongst others, randomized control trials, open-label studies and case-series (Table 2). Qualitative assessment rated four studies as 'Good', six studies as 'Fair' and four studies were rated 'Poor', *see table 2 and supplementary table S2.2.* Baseline characteristics of the included patients were comparable in terms of age, disease, mean symptom duration, and treatment effect (Table 2).

Patient	Sex	Age onset (y)	Education*	Disease duration (y)	Axis I Comor-bidity	Obsessions	Compulsions	Medication History				Previous DBS	Time to last follow-up (m)
								SSRI	Anti-psychotica	Clomipra-mine	Psycho-therapy		
1	Female	15	4	33	MDD	Perfectionism	Cleaning, Ordering, Checking	Venlafaxine	Aripiprazol		CBT	STN	74
2	Female	20	6	20		Fear of contamination	Washing, cleaning	Paroxetine, Cipramil, Sertralin	Olanzapine, Risperidon		CBT		35
3	Female	22	6	31		Fear of contamination, Perfectionism	Cleaning, Counting, Checking	Sertraline, Citalopram, Duloxetine	Quetiapine	Yes	CBT		28
4	Male	13	6	22	MDD, ASD	Fear of harming others	Mental compulsions, washing	Fluoxetine	Quetiapine	Yes	CBT		11
5	Female	29	5	28	MDD	Fear of harm, contamination	Mental compulsions, checking	Sertraline, Paroxetine, fluvoxamine		Yes	CBT		20
6	Male	12	5	45	MDD	Need for order, cleanliness	"Just-Right" behavior	Paroxetine, Venlafaxine, Amitriptyline		Yes	CBT		20
7	Female	6	4	22		Fear of contamination, Fear of harming other	Cleaning, washing, checking, counting	Fluoxetine, Sertralin			CBT		12

*According to the Dutch Verhage classification of education. AN, anorexia nervosa; ASD, autism spectrum disorder; ED, eating disorder; MDD, major depression disorder

Table 1: Patient Characteristics

Authors	Study design	Quality	Year of publication	Number of patients	Mean age at surgery (sd)	Mean symptom duration (sd)	Follow-up (m)	Mean Y-BOCS reduction	Target	Stimulation parameters		
										Frequency (Hz)	Pulse width (μs)	Amplitude (V)
Grassi, et al.	Controlled trial	Good	2018	20	45.7 (12.7)	26.5	n/a	15.0	vALIC	n/a	n/a	n/a
Luyten OFF	Double-blind, randomized, crossover study	Good	2015	24	40.9 (11.0)	n/a	1	6.4	ALIC/ BNST	n/a	n/a	n/a
Luyten ON	Double-blind, randomized, crossover study	Good	2015	24	40.9 (11.0)	n/a	2	17.3	ALIC/ BNST	115	270	6.3
Mallet, et al	Randomised, double-blind, crossover, sham controlled	Good	2008	8	41.3 (7.8)	32.3 (7.1)	11	6.5	STN	n/a	n/a	n/a
OFF-ON	study											
Mallet, et al.	Randomised, double-blind, crossover, sham controlled study	Good	2008	8	46.4 (2.8)	27.4 (8.7)	10	12.9	STN	130	60	< 4
ON-OFF												
Tyagi, et al.	Double-blind, randomized trial	Fair	2020	6	45.4 (10.5)	24.2 (3.9)	n/a	22.0	amSTN & VC/VS	130	60	amSTN: 1.9; VC/VS: 6.4
Huys, et al.	Open-label trial	Fair	2019	20	43.2 (13.8)	28.9 (5.6)	13	10.2	ALIC-Nacc	134	5.12	131.5
Barcia, et al.	Randomized, double-blind, crossover, sham controlled study	Fair	2019	7	36.0	25.3	21	16.9	Nacc/CN	130	60	3.5
Mantione, et al.	Prospective, control-study	Fair	2015	16	42.6 (11.4)	29.0 (12.5)	8	11.8	Nacc	130	90	3.5 -5.0
Jimenez et al.	Cohort study, open protocol	Fair	2009	5	36.8	17.4	12	17.2	ITP	130	450	5
Huff, et al	Double-blind, sham-controlled, crossover study	Fair	2009	10	35.3 (7.0)	22.2 (8.7)	12	6.8	Nacc	145	90	5.5
Greenberg, et al.	Uncontrolled intervention study	Fair	2006	10	35.3	22.5	36	11.6	VC/VS	100 - 130	90 - 210	8.17
Goodman, et al.	Blinded, sham-controlled pilot-study	Poor	2010	6	36.2 (5.0)	24.0 (8.6)	12	12.0	VC/VS	134.2	175	4.75
Grant, et al.	Case report	Poor	2016	1	23.0	5.0	36	23.0	Nacc	n/a	n/a	n/a
Aouizerate, et al.	Case report	Poor	2004	1	56.0	40+	6	1.0	vALIC	130	120	4
Gabriëls, et al.	Case series	Poor	2003	3	41.7	24.5	15-33	15.0	VC/VS	n/a	n/a	n/a

Table 2. Study characteristics. (am)STN, the (anteromedial) subthalamic nucleus; ALIC, the anterior limb of the internal capsule; Nacc, the nucleus accumbens; NC, nucleus caudatus; VC/VS, ventral capsule/ventral striatum; BNST, bed nucleus of the stria terminalis; ITP, inferior thalamic peduncle

Overall results from the literature

A total of 36 neuropsychological tests were used within the 14 studies reporting on cognitive outcome following DBS for OCD. Tests were categorized according to the following cognitive domains: attention and memory, executive functioning, with cognitive flexibility addressed separately, verbal fluency, motor system, intellectual ability and phasia/praxis (Table 3). See the supplementary materials S3 for a brief summary and explanation of the applied neuropsychological tests. In the following section, cognitive outcomes are reported according to study type dichotomized into studies that report the cognitive outcome when stimulation is turned on compared to stimulation turned off (2), controlled intervention studies (6), uncontrolled before-after studies (3) and case-series and reports.(3).

ON-OFF design

In Luyten et al. (2016), after an initial parameter optimization phase, 17 patients completed the double-blind crossover trial with two arms of 3 months each (9 patients ON–OFF and 8 patients OFF–ON) of which 82 % of the patients were stimulated in the bed nucleus of the stria terminalis (BNST), 41 % in BST and/ or in the internal capsule and 35 % in its anterior limb.[19] In a direct comparison, BNST stimulation was more effective than ALIC stimulation; however this difference was significant for the open-label phase only, and not for the crossover phase of the study. Neuropsychological evaluations were performed before surgery and during both crossover phases and analyzed using Friedman/Repeated measures ANOVA. No differences between ON and stimulation OFF were observed for the Wisconsin Card Sorting Test (WCST), Word Fluency Test (WFT) and Raven's Standard Progressive Matrices (RSPM). Except for the Complex Figure Test of Rey (CFTR) - Late Recall (mean [range]) (19 [4-35] vs. 16 [4-34]; p=0.03) there were significant differences between baseline and OFF-phase data indicating slightly improved values during OFF than pre-operatively. Significant lower scores between ON and OFF measurements were found for the SCWT – Chart C (91 [60-136] vs. 105 [58-193]; p < .001) words and the TMT-B (86 [41-210] vs. 97 [42-240]; p < .01), suggesting less interference, improved cognitive flexibility and executive functions. Higher values during stimulation ON compared to the OFF phase were observed for the AVLT – interference list B (7 [1-11] vs. 5 [1-10]; p < .01).
Mallet *et al. (2008)* enrolled 16 patients in a double -blind, cross-over design with two 3-month phases (8 patients ON-OFF/ 8 patients OFF-ON) separated by a 1-month washout period preluded by a period of optimizing the stimulation parameters.[20] Following active STN DBS, YBOCS scores were significantly lower than sham stimulation, independently of the group and the period (mean ±SD, 19±8 vs. 28.7±; p=0.01). Neuropsychological evaluation was performed before surgery and after both crossover phases. No differences between ON-OFF and stimulation OFF-ON stimulation were observed for the included neuropsychological tests: Hopkins Verbal Learning Test (HVLT), TMT, SCWT, Digit Ordering Test (DOT); Digit Symbol Substitution Test (DSST) and Lexical Verbal Fluency Test (LVFT),

where no comparisons were made with baseline values. The authors did not clarify the statistical approach for the neuropsychological data analyses.

Controlled intervention studies

Huff *et al.* (2010) performed a double-blind, sham-controlled crossover study including ten OCD patients, receiving right-sided unilateral STN-DBS. Both OCD-severity and cognitive functioning were assessed at baseline and at one year of follow up.[21] STN-DBS reduced the YBOCS from (mean ±SD) of 32.2±4.0 to 25.4±6.7. No significant changes were observed for the Tower of London (ToL), VF and Continuous Performance Test (CPT) Dprime symbols (S)). The CPT Dprime Numbers (N) improved from (mean ±SD) 0.99±0.53 at baseline to 1.56±0.79 $p<0.05$ as analyzed with the parametric Wilcoxon signed rank test.

In a randomized, sham-controlled study, Goodman *et al* (2010) enrolled six OCD patients to receive DBS of the VC/VS.[22] One month after DBS surgery, patients were randomized for active (3) or sham (3) stimulation for a period of one month succeeded by an open label phase of one year. A mean (±SD) YBOCS reduction of 15.67±11.60 was reported after one year. Cognitive outcome was assessed at baseline, six months and after one year of follow up, where we will limit the discussion of these results at last follow-up. Outcome measurements of the neuropsychological scores were dichotomized into an improvement or decline beyond 90% confidence interval for reliable change and presented for none- vs. responding patients. Therapy response was defined as a >35% reduction of YBOCS scores. Consequently, raw test scores were unavailable. For the non-responding patients; declines were observed for the Wechsler Adult Intelligence Scale (WAIS (1) and the Perdue Pegboard (PP) (1), and improvements were observed for VF (1) and Tower of Londen (ToL) tes (1). Responding patients showed improvements for the ToL (1), the PP (3) and the HVLT (1), a decline was observed for the VF (1).

In a randomized, double-blind, crossover, sham controlled study, Barcia *et al*. (2019) performed DBS surgery on a series of 7 patients with refractory OCD with the intent of identifying an optimal target along the striatum spanning the caudate nucleus and the Nacc by comparing different contact points including a sham stimulation period for three months interspersed with wash-out periods of 1 month.[23] The best contact (BC), was determined for each patient according to lowest achieved YBOCS score. The mean YBOCS improvement for the BC was 51.33%. For neuropsychological functioning, obtained test scores were analyzes using a post-hoc Wilcoxon signed rank test for all stimulation trials. A statistically significant decrease was observed for the TMT-B performance time after stimulation contact points and sham compared to baseline (BL) except the BC. (BL: 155s; C0: 77s ($p=0.018$); C1: 62.5s ($p=0.018$); Sham: 66s($p=0.046$)) [BC: 88s ($p=0.866$)].

Tyagi *et al.* (2020) studied the differential effect of VC/VS and amSTN stimulation in the same patient.[24] Six patients entered the randomized, double-blind, counterbalanced design, with two arms of 3 months each (STN-VC/VS -VS/VS-STN) followed by phases of stimulation of both targets, the optimal target and the optimal target in combination with CBT. Primary outcome analyses (YBOCS) and cognitive assessments were performed at baseline, and

after each phase. YBOCS scores at follow-up reduced a significant percentage at the end of all phases. Stimulation of both the STN and the VC/VS was associated with significant improvements over baseline (baseline: 36.7±0.75; amSTN 19.8 ±4.32 ($p<0.001$); VC/VS 17.0 ±3.57 ($p <0.001$) ($p = .020$ and $p = .012$, respectively). However, there was no significant difference when comparing the amSTN and VC/VS against each other. For cognitive performance, a significant effect was observed as an improvement in EDS errors of the Intra/Extradimensional Set Shift (IED) task after amSTN stimulation, compared to baseline ($p <0.003$) and VC/VS stimulation ($p <0.018$).

In a case-control study by Mantione *et al.* (2015), 16 patients with refractory OCD received Nacc DBS and were compared to OCD patients receiving treatment as usual.[6] After eight months of follow-up, YBOCS scores substantially decreased in the OCD-DBS group (mean ± SD) (- 15.7 ± 10.8). Cognitive performance was evaluated by assessment of multiple tests; Raven's Advanced Progressive Matrices Test (RAPM), The California Verbal Learning test (CVLT), DSST, Rey Complex figure test (RCFT), SCWT, VF, TMT (A and B), WCST, ToL, Digit Span Test (DSpT), and PP, at baseline, 3 weeks and 8 months postoperatively. A linear mixed model analysis was performed to assess changes over these three different time points. At baseline, no significant differences were observed for all tested cognitive variables, except for a lower score on the DSST in the OCD-DBS group. After eight months of follow-up, a reduced performance on the RCFT and RAPM was observed for the OCD-DBS group, compared to controls.

Grassi *et al.* (2018) assessed impulsivity and decision making in 20 OCD patients receiving vALIC DBS, compared to healthy controls and conventional OCD treatment.[25] Total YBOCS scores decreased from (median (interquartile range) 32.5 (30–35) to 17.5 (12–20.5) for the DBS treated patients and 29.5 (21.5–34) to 19 (11–22) for the patients treated as usual. Decision-making performances and impulsivity were evaluated under the ambiguity on the Iowa Gambling Task (IGT) and the Beads Task (BT) respectively. Although baseline scores were absent, OCD patients receiving either DBS (median; [interquartile range]) (–11 [–42; –1], $p=0.011$) or treatment as usual (–4 [–35; 15]), $p=0.037$) scored lower on the IGT compared to healthy controls (10 [–5; 28]), suggesting an impaired decision-making. In analogy, OCD-DBS patients (median, no range available)) (3, $p=0.008$) and patients treated (2, $p<0.001$) as usual required less draws to decision compared to healthy controls implicating high impulsivity.

Uncontrolled before- after studies

In an uncontrolled intervention study by Greenberg *et al.* (2006), DBS of the VC/VS was performed in ten patients with treatment refractory OCD.[26] Eight out of ten patients reached the three year follow up measurements. Following VC/VS stimulation the YBOCS score decreased from (mean ±SD), 34.6±0.6 at baseline to 22.3±2.1 three years post-surgery. Neuropsychological assessments were performed at baseline and after a mean of ten months constant DBS. Although no specific applied tests or data was presented, Greenberg *et al* describe no pervasive pattern of decline or improvement on an individual level. On a goup level, scores for the recall of prose passages improved.

Jiménez *et al.*(2009) conducted an open protocol study in five OCD patients to determine the safety and efficacy of DBS of the ITP. Clinical changes including cognitive functioning were assessed assignments every three months for 12 months and compared to baseline.[27] The cognitive assignments included verbal memory tests, non-verbal memory tests, Manual/ Motor Praxis Test (MPT), WAIS, WCST, Finger Tapping Test (FTT), VF, SCWT and the Token Test (TT). After 1 year of active ITP-DBS the mean Y-BOCS decreased from 35 to 17.8 p=0.001. No raw data or statistical methods were provided for the cognitive tests. However, no changes on neuropsychological tests were observed at any moment of follow-up, compared to baseline.
Huys *et al.*(2019) enrolled 20 patients with OCD in an naturalistic open-label study over 1 year to receive ALIC-Nacc DBS.[28] Cognitive outcome data was acquired at six- and twelve months of stimulation, which included the ToL, CPT, SCWT and the Go/No-Go test. At last follow-up the mean YBOCS reduction was 33.33%±21.50, and 40% of the patients were considered responders. No significant results were found on cognitive performance at both follow-up moments compared to baseline as analyzed using a Friedman test.

Case series and case reports

Gabriëls *et al.*(2003) reported on three cases of patients with refractory OCD, that received bilateral DBS of the VC/VS.[29] Following active stimulation for one year, YBOCS scores reduced with more than 35% in two patients. However, one patient showed no significant treatment effect and underwent capsulotomy at 15 months post-implantation. Neuropsychological tests were assessed at baseline and after one year of follow up. Applied tests were the RSPM, Paced Auditory Selective Attention Test (PASAT), RCFT, DSpT, Spatial Span Test (SST), DSST, WFT, ToL and WCST. Whereas no decline in cognitive outcome was observed, one case showed improvement on the RSPM, PASAT, CFR and the learning subset of the DSST, with significant change defined as more than 2 SD change compared to baseline.
In a case-report of Aouizerate *et al.*(2004), one OCD patient received DBS of the ALIC. OCD symptom severity and neuropsychological scores were assessed at baseline and at one, and six months postoperatively.[30] The YBOCS scores decreased substantially after nine months of follow up (30 vs 16). Performance on memory tasks i.e. Benton Visual Retention Test (BVRT) and The Free and Cued Selective Reminding Test (FCRST) improved at one month of follow-up and improvement remained at six months. In attentional and executive functions, the TMT-B and WCST scores improved substantially (87.5 and 66.0%, respectively), while a slight reduction was observed in the VF task. TMT-A, SCWT, and Zazzo cancellation task (ZCT) scores remained equal.
Grant *et al.*(2016). present a case report of a therapy-refractory OCD patient, receiving Nacc DBS.[31] Cognitive performance was determined at one, two, and three years of follow-up and assessed by the Stop-signal reaction time (SSRT) and IED. YBOCS reduction debuted after the first eight months of stimulation and remained over the course of three years. For all applied tests, performance improved at three years of follow-up compared to baseline.

Table 3. Overview of the results of the neuropsychological assessment per study with electrical stimulation on. BL: baseline; W: week; M: month; Y: year; n/a: not available; ns: not significant. Abbreviations and explanation of all applied tests can be consulted in the supplementary material.

Domain	Study	Time of measurement	Measure types	Results[a]
Attention & Memory	Mantione, et al.	3 (BL, W3, M8)	CVLT, DSpT, RCFT; CPT; DSST	RCFT (copy): decline; CVLT: improvement; DSST: improvement₹
	Aouizerate, et al.	3 (BL, M1, M6)	BVRT, FCSRT	BVRT: improvement; FCSRT; improvement¿
	Goodman, et al.	3 (BL, M6, M12)	HVLT	Improvement in 1 patient*
	Barcia, et al.	2(BL, M12)	FCSRT; LNST	ns
	Luyten, et al. ON	2 (BL, M2)	RCFT; RAVLT	RCFT (recall): improvement; RAVLT: Improvement
	Luyten, et al. OFF	2 (BL, M2)	RCFT; RAVLT	ns
	Jimenez et al.	6 (BL, M1, M3, M6, M9, M12)	VMT; N-VMT;	ns
	Mallet, et al ON-OFF	3 (BL, M3, M6)	HVLT; DOT; DSST	ns ?
	Mallet, et al. OFF-ON	3 (BL, M3, M6)	HVLT; DOT; DSST	ns ?
	Gabriëls, et al.	2 (BL, M12)	DSpT; RCFT; SSP; PASAT	RCFT: Improvement +
	Huff, et al.	2 (BL, M12)	CPT	CPT (Dprime N): improvement ₽
	Huys, et al.	2 (BL, M12)	Go/No-Go Task	ns
Executive functioning	Mantione, et al.	3 (BL, W3, M8)	ToL; RAPM	ToL: improvement ₹RAPM: decline
	Aouizerate, et al.	3 (BL, M1, M6)	ZCT	ns
	Goodman, et al.	3 (BL, M6, M12)	ToL	ToL: mixed response*
	Huys, et al.	2 (BL, M12)	ToL; SSRT	ns
	Gabriëls, et al.	2 (BL, M12)	RSPM; ToL	RSPM: improvement +
	Grassi, et al.	2(BL, N/A)	IGT; BT	ns Ψ
	Luyten, et al. ON	2 (BL, M2)	RSPM	ns
	Luyten, et al. OFF	2 (BL, M2)	RSPM	ns
	Huff, et al.	2 (BL, M12)	ToL	ns ₽
	Grant, et al.	4 (BL, Y1, Y2, Y3)	SSRT	Improvement †
Cognitive flexibility	Mantione, et al.	3 (BL, W3, M8)	SCWT; TMT-A; TMT-B; WCST	SCWT: improvement; WCST (% perseverative errors): improvement ₹
	Aouizerate, et al.	3 (BL, M1, M6)	WCST; TMT-A; TMT-B	WCST: improvement; TMT-B: improvement
	Huys, et al.	2 (BL, M12)	SCWT; TMT-A; TMT-B	ns
	Barcia, et al.	2(BL, M12)	SCWT; TMT-A; TMT-B; WCST	TMT-B: improvement
	Luyten, et al. ON	2 (BL, M2)	SCWT; TMT-A; TMT-B; WCST	SCWT: improvement; TMT-B: improvement
	Jimenez et al.	6 (BL, M1, M3, M6, M9, M12)	SCWT, WCST	ns
	Luyten, et al. OFF	2 (BL, M2)	SCWT; TMT-A; TMT-B; WCST	ns
	Mallet, et al ON-OFF	3 (BL, M3, M6)	SCWT; TMT-A; TMT-B	ns ?
	Mallet, et al. OFF-ON	3 (BL, M3, M6)	SCWT; TMT-A; TMT-B	ns ?
	Gabriëls, et al.	2 (BL, M12)	WCST	ns +
	Grant, et al.	4 (BL, Y1, Y2, Y3)	IED	improvement †
	Goodman, et al.	3 (BL, M6, M12)	WCST	ns
	Tyagi, et al.	2 (BL, W60)	IED	STN stimulation: improvement

Table 3. *Continued*

Domain	Study	Time of measurement	Measure types	Results[R]
Verbal	Jimenez, et al.	6 (BL, M1, M3, M6, M9, M12)	VFu	ns
fluency	Mantione, et al.	3 (BL, W3, M8)	VFu	Semantic(occupations): improvement ₹
	Aouizerate, et al.	3 (BL, M1, M6)	VF (IST)	ns
	Goodman, et al.	3 (BL, M6, M12)	VFu	mixed response*
	Barcia, et al.	2(BL, M12)	VFu	ns
	Huff, et al.	2 (BL, M12)	VF(VFE)	ns
	Luyten, et al. ON	2 (BL, M2)	WFT	ns
	Luyten, et al. OFF	2 (BL, M2)	WFT	ns
	Gabriëls, et al.	2 (BL, M12)	WFT	ns +
	Mallet, et al.ON-OFF	3 (BL, M3, M6)	LVFT	ns⁉
	Mallet, et al.OFF-ON	3 (BL, M3, M6)	LVFT	ns⁉
Motor	Mantione, et al.	3 (BL, W3, M8)	PP	ns ₹
system	Goodman, et al.	3 (BL, M6, M12)	PP	mixed response*
	Jimenez, et al.	6 (BL, M1, M3, M6, M9, M12)	FTT	ns
Visuospatial perception	Jimenez et al.	6 (BL, M1, M3, M6, M9, M12)	VCT (WAIS)	ns
Intellectual ability	Goodman et al.	3 (BL, M6, M12)	WAIS	Ns*
Phasia/ Praxis	Jimenez, et al.	6 (BL, M1, M3, M6, M9, M12)	TT; MPT	ns
Not specified	Greenberg, et al.	2 (BL, M10)	**	Recall improvement

[R] Results are based on measurement at last moment of follow-up.

U Undefined

¿ Results are presented as how they were described in the study result section.

₹ No significance was calculated for change in performance in DBS-cohort between last moment of follow-up and baseline, therefore we chose a value of change of more than 2 (regardless of unit) to be of substantial difference to report.

† Performance is based on comparison of outcomes to a healthy control group.

* Performance improvement was based on a change beyond the 90% CI between baseline and follow-up.

** Neuropsychological battery including measures of IQ, visual motor speed and mental flexibility, verbal and visual learning, memory, and conceptual reasoning.

⁉ Significance change is based on between-group differences in active and sham stimulation.

Ψ Results of performance change from baseline compared to follow-up were combined for TAU-OCD and DBS-OCD.

₽ Neuropsychological tests were assessed in 7 of a total of 10 patients.

+ Performance improvement was based on a change of more than 2SD between BL and follow-up.

A case series of cognitive outcome ofVC/VS stimulation

Seven patients receivingVC/VS receivingVC/VS stimulation for refractory OCD in our own clinic received a protocolized neuropsychological examination at baseline and at follow-up. The mean follow-up time was 18 months ±8.6 (SD). For individual stimulation settings at time of follow-up, see supplementary material S.4. No significant changes in the performance on the BNT,VF, RAVLT (total learning and recall) and SCWT were observed after a median follow-up of 18 months of VC/VS stimulation, we also refer to the S.4 for an individual outcome analyses.

The TMT ratio showed a statistically significant increase, resulting from a decrease in the TMT-A -7.37 ± 7.27 seconds (p=0.043) and a trend toward an increase in TMT-B 9.59 ± 12.14 seconds (p=0.063), with an effect size of 0.63. When compared, no differences were found in all outcome variables between non- responding and responding patients.

Table 4: Cognitive outcome of VC/VS stimulation for OCD in an institutional cohort. *p< 0.05.

Test	Baseline [±SD]	Follow-up [±SD]	Mean difference	P-value	Effect size
YBOCS	33.86 ± 2.91	23.29 ± 8.01	10.57 ± 8.5	0.017*	
Boston Naming test	26.0 ± 4.51	26.75 ± 2.75	2.5 ± 6.8	0.684	0.12
Semantic verbal fluency					
Animals and occupations	43.71 ± 12.58	40.57 ± 9.03	-3.14 ± 7.69	0.499	-0.18
Phonetic verbal fluency					
Letters D, A and T	32.29 ± 6.90	33.14 ± 10.57	0.85 ± 10.48	0.735	0.09
Rey auditory verbal learning test					
Total	53.57 ± 8.46	50.43 ± 6.40	-3.86 ± 7.69	0.310	-0.38
Recall	11.29 ± 1.60	11.0 ± 1.46	-0.43 ± 0.97	0.257	-0.42
Trail making test					
Time A	37.90 ± 10.24	28.66 ± 8.68	-7.37 ± 7.27	0.043*	-0.77
Time B	87.94 ± 26.64	95.11 ± 35.65	9.59 ± 12.14	0.063	-0.70
Time B / Time A	2.43 ± 0.87	3.37 ± 1.60	0.94 ± 0.95	0.018*	0.63
Stroop color word test					
Color-word card – color card	32.37 ± 15.98	31.82 ± 20.39	1.15 ± 8.63	0.612	-0.14

Discussion

To study the cognitive safety of DBS for OCD, we conducted a systematic review of the literature and presented the cognitive outcome both of which have limitations. Our, clinical findings should be interpreted within the limits of this small-sized retrospective open case study, lacking randomization and non-blinded assessment which may therefore be prone for systematic bias. Further, patients had continuous medication and psychotherapy during the follow-up of the study. Therefore, a confounding effect of co-treatment cannot be ruled out. Second, the systematic review was limited by diversity of the applied neuropsychological tests, heterogeneous study-designs incl. follow-up time, variable data presentation and statistical processing. The overall (target specific) effect of DBS for OCD could therefore not further be examined as we could not perform a meta-analyses (*see supplemental table S5 for a target orientated presentation of significant changes in cognitive outcome)*. However, both the case series and individual studies show interesting outcomes on several cognitive domains. As for the systematic review, we will qualitatively discuss the cognitive outcomes according to the corresponding domains and aim to isolate a cognitive pattern through which the efficacy of electrical stimulation for OCD might be explained, by only consider studies that were rated as 'Fair' or 'Good' according to the National Heart, Lung and Blood Institute (NIH) quality assessment tools, *see table 2 and supplemental material 2.2-2.3*.[11]

Attention and memory

Sustained attention and response inhibition, as assessed by the CPT or the DSST, improved following stimulation of the Nacc.[6,19] Interestingly, it is hypothesized that neuropsychological impairment in itself may be considered as a epiphenomena in OCD patients since the overflow of obsessive thoughts could cause an overload on the executive system, resulting in neurocognitive impairments.[32] Nevertheless, exploratory correlation analyses did not reveal any association between cognitive impairment and the improvement of OCD symptoms following Nacc DBS.[6]

In contrast with verbal memory tasks, lower performance on non-verbal memory tasks such as the RCFT, were more consistent in OCD patients.[33,34] The RCFT is used to obtain information on non-verbal, visual memory (immediate/ late recall score) and provides and reflects a person's visuospatial organization (copy score).[35] The immediate/late recall score showed improvement, whereas copy scores decline following stimulation of the BNST/ALIC and Nacc respectively.[6,19] These differential results within the RCFT could be explained as a direct cause of improved memory functions and as a result of dysfunctional organizational strategies.[33,35]

Executive functioning

Executive functioning refers to a domain of cognitive abilities that enable and drive one's adaptive, and goal-directed behavior.[36] Neuropsychological studies comparing OCD patients with healthy controls show ambiguous results considering tests on planning ability such as the ToL tests, similar to the studies included in the present review.[33] [6] Lower RAPM scores are observed when comparing OCD patients stimulated with DBS to a control group of OCD patients receiving CBT.[6] This inter-group difference is however based on a substantial interval between a small decline in one group (DBS), and small improvement in another (control). Since the lacking of statistical quantification of the ToL improvement in Mantione *et al* and the poor quality of the three other studies that indicate an improvement in executive functioning, it is inconceivable to validly conclude that DBS improves executive functioning in OCD patients.[31,6,22,29]

Cognitive flexibility

OCD patients often have difficulties in shifting between mental processes that generate behavioral responses, indicating a form of rigidness or cognitive inflexibility.[33,37] Cognitive flexibility is defined as the ability to flexibly adjust behavior to the demands of a changing environment and has been considered as a putative endophenotype of OCD.[38] Different aspects of cognitive inflexibility i.e. attentional set shifting, reversal and alternation, inhibition of prepotent response and cued task switching paradigms, cognitive control measures have been probed in OCD patients using a variety of tests including the SCWT, WCST, (TMT-A/B) and the (IED) task.[39] Contrary to our case series, Luyten *et al.* observe an improvement of both TMT-A and TMT-B indicating better performance of visual search, scanning, speed of processing and cognitive flexibility.[19] Likewise, Barcia *et al,* observe an improvement of TMT-B scores compared to pre-surgical evaluation after stimulation of contact 0 and 1 and, interestingly, sham stimulation. TMT-B performance at stimulation at best contact however, was different from baseline.[23] Modulated cognitive flexibility is further supported by decreased interference scores (Stroop C – B) on the SCWT as shown by Luyten *et al.*[19] In the study Tyagi *et al,* in which 6 OCD patients received VC/VS or amSTN stimulation in counterbalanced phases, amSTN stimulation (but not VC/VS stimulation), was associated with improved extra dimensional errors within the IED, enhancing the ability to shift attention away from the previously correct stimulus dimension to a different dimension.[24] Considering the mixed population of OCD OCD (n=2) and MDD (n=12), the study by Widge *et al.* was excluded from this review. However, they showed that VC/VS stimulation enhanced performance on an affective Multi-Source Interference Task thereby improving cognitive flexibility.[40]

Case series

The patients described in the case series are comparable to the existing literature in terms of baseline characteristics, stimulation parameters and treatment efficacy. After a mean follow-up time of 18-months the TMT ratio significantly worsened, which has not been reported by other studies included in the systematic review or in OCD patients receiving conventional treatment.[41] A prolonged TMT – B / TMT – A ratio suggests an acquired set switching deficit. The absence of other significant changes on other neuropsychological tests and results in the case series, suggest the relative safety of DBS treatment of OCD.

Conclusion

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. Further, the data was too inconsistent to recognize a cognitive pattern that is associated with better outcome or would (in part) explain the efficacy of deep brain stimulation for OCD. However, in contrary to our case series, multiple studies report on an improvement of cognitive flexibility regardless of the stimulation target. We recommend that 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.

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Supplementary material

S1. Search strategy

All database searches were performed in November 2020.

S1.1 PubMed search strategy

1	"obsessive compulsive disorder"[MeSH Terms]	14,849
2	"obsessive compulsive disorder*"[Title/Abstract]	13,653
3	"Obsessive compulsive behaviour"[Title/Abstract]	88
4	"obsessive-compulsive disorder"[Title/Abstract]	13,08
5	"Obsessive-compulsive behavior"[Title/Abstract	240
6	"Obsessive-compulsive behaviour"[Title/Abstract]	88
7	"Obsessive compulsive behavior"[Title/Abstract]	240
8	"obsessive compulsive neuro*"[Title/Abstract]	183
9	"neurotic disorder*"[Title/Abstract]	831
10	"Neurosis"[Title/Abstract]	4,669
11	"psychoneurotic disorder*"[Title/Abstract]	56
12	psychoneurosis[Title/Abstract]	352
13	obsession*[Title/Abstract]	4,134
14	compulsion*[Title/Abstract]	2,765
15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	27,731
16	"deep brain stimulation"[MeSH Terms]	8,997
17	"deep brain stimulation*"[Title/Abstract]	11,836
18	"Electrical stimulation of the brain"[Title/Abstract]	318
19	"Electrical stimulation"[Title/Abstract]	46,279
20	"brain stimulation"[Title/Abstract]	17,437
21	"stimulat*"[Title/Abstract]	1,161,665
22	"stimuli*"[Title/Abstract]	226,47
23	"stimulu*"[Title/Abstract]	169,79
24	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	1,432,822
25	English[Language]	27,291,135
26	humans[MeSH Terms]	18,973,025
27	#15 AND #24 AND #26 AND #27	1,291

S1.2 Cochrane search strategy

#1	"obsessive compulsive disorder*":ti,ab	2040
#2	MeSH descriptor: [Obsessive-Compulsive Disorder] explode all trees	1045
#3	"obsessive-compulsive disorder":ti,ab	2040
#4	"anankastic personal*":ti,ab	0
#5	"obsessive-compulsive behavior":ti,ab	28
#6	"obsessive compulsive behavior":ti,ab	28
#7	"obsessive compulsive neuro*":ti,ab	0
#8	"obsessive-compulsive neuro*":ti,ab	0
#9	"neurotic disorder":ti,ab	20
#10	neurosis	1152
#11	"psychoneurotic disorder*":ti,ab	0
#12	"psychoneurosis":ti,ab	19
#13	"obsession*":ti,ab	141
#14	"compulsion":ti,ab	148
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	3554
#16	MeSH descriptor: [Deep Brain Stimulation] explode all trees	289
#17	"deep brain stimulation":ti,ab	1100
#18	"electrical stimulation of the brain":ti,ab	15
#19	"brain stimulation":ti,ab	2586
#20	"electrical stimulation":ti,ab	5395
#21	"stimulat*":ti,ab	4
#22	"stimuli*":ti,ab	16572
#23	"stimulu*":ti,ab	2
#24	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	23957
#25	#15 AND #24	196

S1.3 EMBASE search strategy

(deep brain stimulation.ec. or brain stimulation.ab. or electrical stimulation of the brain.ab. or electrical stimulation.ab. or stimulat*.ab. or stimuli*.ab. or stimulu*.ab.) and (obsessive compulsive disorder.ec.) or Neurotic disorder*.ab. or Neurosis.ab. or psychoneurotic disorder*.ab. or Psychoneurosis.ab. or Obsession*.ab. or Compulsion*.ab. or obsessive-compulsive disorder.ab. or obsessive-compulsive behavior.ab. or obsessive compulsive behavior.ab. or obsessive compulsive neuro*.ab. or obsessive-compulsive neuro*.ab.)

S1.4 Psycinfo search strategy

AB(obsessive compulsive disorder OR obsessive-compulsive disorder OR OCD OR neurotic disorder OR psychoneuro* OR neurosis OR psychosis OR obsession* or compulsoion* OR obsessive-compulsive behavior OR obsessive-compulsive behaviour) AND AB(deep brain stimulation OR DBS OR electrical stimulation OR brain stimulation OR stimuli* OR stimulatu* or stimulat*)

S.2 Qualitative assessment

CD: cannot determine, NA: not applicable, NR: not reported. Overall score: Good/Fair/Poor, according to the NIH quality assessment protocol.

S.2.1. Quality assessment case series and case reports

Criteria	Gabriëls *et al.*	Aouizerate *et al.*	Grant *et al.*
Was the study question or objective clearly started?	Yes	Yes	No
Was the study population clearly and fully described, including a case definition?	Yes	Yes	Yes
Were the cases consecutive?	Yes	NR	NR
Were the subjects comparable?	Yes	NA	NA
Was the intervention clearly described?	CD	Yes	No
Were the outcome measures clearly defined, valid, reliable, and implanted consistently across all study participants?	Yes	Yes	Yes
Was the length of follow-up adequate?	Yes	No	Yes
Were the statistical methods well-described?	No	NA	No
Were the results well-described?	CD	Yes	Yes
Qualtiy rating	Poor	Poor	Poor
Rater #1	M.V.	M.V.	M.V.
Rater #2	T.B.	T.B.	T.B.

Additional comments

Gabriëls *et al.*: Stimulation parameters for the intervention were not given, intervention was further fully described. Only 3 cases were included, in which 1 patient got full explantation at M15 and capsulotomy instead. Results were briefly described and no statistical significance was calculated.

Aouizerate *et al.*: Follow-up period was 'only' 6 months, which is relatively short compared to other studies. Results were well-described, but no statistical tests were performed on neuropsychological outcomes, since n=1.

Grant *et al.*: Study is an extension in follow-up of an earlier case report, both studies are approached for this qualitative analysis, no statistics are performed since n=1.

S.2.2. Quality assessment of controlled intervention studies

Criteria	Barcia, *et al.*	Tyagi, *et al.*	Huff, *et al.*	Mallet, *et al.*	Luyten, *et al.*	Mantione, *et al.*	Goodman, *et al.*	Grassi, *et al.*
Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	Yes	Yes	No	Yes	Yes	No	Yes	No
Was the method of randomization adequate (i.e., use of randomly generated assignment)?	Yes	Yes	NA	Yes	Yes	NA	NR	NA
Was the treatment allocation concealed (so that assignments could not be predicted)?	NR	Yes	NA	NR	NR	No	NR	NA
Were study participants and providers blinded to treatment group assignment?	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Were the people assessing the outcomes blinded to the participants' group assignments?	Yes	NR	Yes	Yes	Yes	No	Yes	No
Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Was there high adherence to the intervention protocols for each treatment group?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	No	No	No	Yes	No	No	No	No
Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	No	No	No	No	No	No	No	Yes
Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	NR	NR	NR	NR	NR	NR	NR	NA
Quality rating	Fair	Fair	Fair	Good	Good	Fair	Poor	Good
Rater #1	M.V.	M.V.	M.V.	M.V.	M.V.	M.V.	M.V.	M.V.
Rater #2	T.B.	T.B.	T.B.	T.B.	T.B.	T.B.	T.B.	T.B.

Additional comments

Mallet: Significancy was calculated as change in NPO between active and sham stimulation in on-off and off-on group.

Luyten: After cross-over period, patients and researchers were unblinded. Statistical analysis was performed with and without correction for multiple testing.

Mantione: Statistical significance was only calculated for intergroup differences, not for baseline/follow-up differences in DBS group, which is of our particular interest.

Goodman: Considered poor for combination of small sample size (6 patients) and no statistical/numerical display of results.

Grassi: All DBS-OCD patients received CBT, but only 8/40 TAU patients. Intervention with DBS proceeded before the study start.

S.2.3. Quality assessment of uncontrolled before-after studies

Criteria	Greenberg *et al.*	Jimenez *et al.*	Huys *et al.*
Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes
Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes	Yes
Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes	Yes
Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Yes	Yes
Was the sample size sufficiently large to provide confidence in the findings?	No	No	No
Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	Yes
Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes	Yes
Were the people assessing the outcomes blinded to the participants' exposures/interventions?	CD	No	No
Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes, no	Yes	No
Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes, NR	Yes, yes	Yes, Yes
Were outcome measures of interest taken multiple times before the intervention and/or multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes	No	Yes
Were the outcome assessors blinded to the exposure status of participants?	No	No	No
If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Yes	No	No
Rating	Fair	Fair	Good
Rater #1	M.V.	M.V.	M.V.
Rater #2	T.B.	T.B.	T.B.
Additional comments	Statistics not described.		

S.3 Neuropsychological tests

S.3.1. Memory

California Verbal Learning Test The California Verbal Learning test (CVLT) is a multi-trial recall and recognition word list learning test based on the popular Auditory Verbal Learning Test. The test is composed of 5 trials during which 16 nouns are read aloud and the subject is asked to recall as many words, in any order.[1] The CVLT claims to measure a broad range of theoretical constructs including free and cued recall, serial position effects, semantic clustering, intrusions, interference and recognition.[2]

Rey Complex Figure Test The Rey Complex figure test (RCFT) assesses a broad range of cognitive abilities including planning, organization and fine motor skills.[5] The subject is presented with a complex geometrical figure as the stimulus. The subject is as asked to draw a copy of the presented figure as accurately as possible, which is followed by a distraction and recall sequence which is repeated twice.[5]

Benton Visual Retention Test The Benton Visual Retention Test (BVRT) The procedure requires drawing responses from the examinee. More specifically, each of 10 abstract

geometric designs is displayed for 10 seconds and then withdrawn. Immediately afterwards the participant is required to reproduce the design from memory.[6] The two scoring systems involve the recording of the total number of designs correctly reproduced in an all-or-none fashion (0–10) and the total number of errors committed. The BVRT assesses visual perception, immediate visual memory and visual-constructive ability.[6]

Free and Cued Selective Reminding Test The Free and Cued Selective Reminding Test (FCSRT) is designed for memory testing. The test begins with a study phase, which is designed to control attention and cognitive processing for the identification of memory impairment that is not secondary to other cognitive deficits. In this phase, pictured items need to be identified in response to category cues. In the test phase, subjects are asked to recall the items they learned. Category cues are used for cued recall, when items cannot be retrieved by free recall. A total recall sum is termed from the sum of free and cued recall. This total recall score is used to access memory performance.[7 8]

Rey Auditory Verbal Learning Test The Rey Auditory Verbal Learning Test (RAVLT) is a widely-used and valid assessment of auditory verbal learning and memory. Total learning was defined as the sum of Trials 1 through 5.

Hopkins Verbal Learning Test The Hopkins Verbal Learning Test (HVLT) is used to assess the verbal learning and memory. The test consists of three trials of free-recall of a 12-item, semantically categorized list. Then a list of 24 words is read and the patient is asked to answer yes or no to each word that was or was not present on the recall list.[9]

S.3.2. Working memory

Digit Span Test Measures of forward and backward digit span (DSpT) are among the oldest and most widely used neuropsychological tests of working verbal memory. In each case, digit span is measured for forward- and reverse-order (backward) recall of digit sequences. Digit sequences are presented beginning with a length of 2 digits, and two trials are presented at each increasing list length. Testing ceases when the participant fails to accurately report either trial at one sequence length or when the maximal list length is reached (9 digits forward, 8 backward). The total number of lists reported correctly is combined across forward span (FS) and backward span (BS) to produce a Wechsler Adult Intelligence Scale (WAIS) total correct score.[3,4]

Letter-Number Sequencing Task The Letter-Number Sequencing Task (LNST) is included as a part of the WAIS. It is a traditionally orally administered test. A participant hears a series of letters and digits and then needs to report back the stimuli with the letters in alphabetic order and digits in ascending numerical order. Performance on the LNST is used to assess the working memory capacity.[10]

Digit Ordering Test The Digit Ordering Test (DOT) is indicated for the assessment of the verbal working memory. For this case, a series of seven digits have to be memorized and immediately recalled in ascending numerical order. The numbers are presented in seven digits in 5 seconds and the test consists of 15 items. Every correct absolute position of a digit scores one point.[11]

Spatial Span Test In the Spatial Span Test (SSP), participants must reproduce sequences of blocks in the order touched by the examiner until two trials are missed at the same sequence length. The examiner records either the maximum number of blocks correctly reported or the total number of correct lists. The SST is frequently considered a nonverbal analogue of the Digit Span Test, which measures the capacity of visuospatial memory.[12]

S.3.3. Attention

Continuous Performance Test The Continuous Performance Test (CPT) measures a person's sustained and selective attention. There is not a single continuous performance test (CPT) test, as a number of commercially available and research CPT tasks exist. The common characteristic of all CPT tests is that they involve sequential presentation of alphanumerical stimuli over an extended period of time.[13]

Digital Symbol Substitution Test The Digit Symbol Substitution Test (DSST) is a paper-and-pencil cognitive test presented on a single sheet of paper that requires a subject to match symbols to numbers according to a key located on the top of the page. Good performance on the DSST requires intact motor speed, attention, and visuoperceptual functions, including scanning and the ability to write or draw (i.e., basic manual dexterity).[14]

Paced Auditory Selective Attention Test The Paced Auditory Selective Attention Test (PASAT) is a test requiring attention and vigilance. In this test, the patient listens to a tape recording of digits presented one at a time. The task for the patient is to add each number to the one immediately preceding it.[15]

S.3.4 Executive functioning

Tower of London test The Tower of London (ToL) tests executive planning proficiency, incorporating delineation, organization, and integration of behaviors needed to achieve a goal. The original ToL consisted of three wooden rods of different lengths, mounted on a block base. Three balls (red, green and blue) were placed on the rods in a prescribed start position. For each problem, the three balls had to be moved from the starting configuration to a target position in the minimum number of possible moves.[16]

Raven's Advanced Progressive Matrices Test The Raven Advanced Progressive Matrices Test (RAPM) tests consists of a series of homogeneous, progressively more difficult items that require a pattern series presented across three rows of designs. The RAPM assesses higher-order general mental ability specifically logical reasoning.[17]

Raven's Standard Progressive Matrices test A version of the Raven test, see Raven's Advanced Progressive Matrices Test.

Isaacs set test The set test is a simple rapid test of mental function which requires the subject to recall items in four different common categories. It is a rapid test of mental function.[18]

Zazzo cancellation task The Zazzo cancellation task (ZCT); it consists in crossing out as rapidly and accurately as possible target symbols.[19]

Stop Signal Reaction Time The stop-signal reaction time (SSRT) task is well established as a paradigm for measuring response inhibition and volitional control in humans. The SSRT task, tests one's ability to suppress an ongoing or already initiated response upon receiving a stop signal. In the SSRT, the participant is repeatedly exposed to a 'go' stimulus and asked to elicit a specific response, such as quickly pressing a button on a keyboard.[20]

Go/No-Go test There are different versions available for the Go/-No Go test. The communal task in the different variants is that subjects are continuously provided either one of two stimuli in random order, in which they need to respond to one of these, but withhold the response to the alternative.[21] The goal of this test is to assess one's behavioral inhibition and impulsivity.[22]

Iowa Gambling Task The Iowa Gambling Task (IGT) is designed for the assessment of decision-making abilities in patients with brain injury of the ventromedial prefrontal cortex (VMPFC). Participants need to choose from four decks of playing cards that unpredictably yield wins and losses, and are instructed to maximize winnings by choosing cards repeatedly. Decks A and B have higher reward cards ($100) than decks C an D, but also yield large penalties. Playing from decks A and B leads to an overall loss, playing from decks C and B leads to an overall gain. Participants should normally start to avoid decks A and B after a few losses and understand the logic behind the allocation. Participants that do not, have poor decision-making processes, which is evident for disorders in the brain reward system, majorly located in the VMPFC.[2324]

Beads Task With the Beads task (BT), a participants' ability to probablistic reasoning is examined. Participants are shown two transparent containers filled with coloured beads in different reciprocal proportions.[25] The containers will then be removed from view and a random sequence of beads will be drawn from one container, with subsequent replacement. It is then for the participant to decide which container the beads are being drawn from. It is often used to assess the jumping to conclusions (JTC) bias as a form of cognitive reasoning biases.[26]

S.3.4.1 Cognitive flexibility

Stroop color word test The Stroop Color and Word Test (SCWT) assesses the ability to inhibit cognitive interference, which occurs when the processing of a stimulus feature affects the simultaneous processing of another attribute of the same stimulus.[16,5] It is believed that the SCWT measures both cognitive flexibility and the ability to inhibit a dominant response.[17] The interference score was calculated according to the classical method, the score derived from the color-word card 3 was subtracted from the score on the color card 2.[18]

Trail Making Test The Trail Making Tests (TMT) consists of two parts.[14] The first part (TMT-A) is thought to provide a baseline measure of psychomotor speed, attention, visuospatial search and target-directed motor tracking. The TMT-B is supposed to be matched to the TMT-A for low-level processes with an additional demand of set-switching. To isolate the latter component, corrected TMT-B scores were derived by obtaining the ratio between TMT – B / TMT – A.[15]

Wisconsin Card Sorting Test The Wisconsin Card Sorting Test (WCST) consists of two card packs having four stimulus cards and 64 response cards in each. The cards depict various geometric shapes in different colors and numbers. The participants are expected to accurately sort every response card with one of four stimulus cards through the feedback (right or wrong) given to them based on a rule.[27] The test provides a measure for attention, perseverance, working memory, abstract thinking, cognitive flexibility, and set shifting.

Intra-Extra Dimensional Set-Shift Task The Intra-Extra Dimensional Set-Shift task assesses the process involved in categorizing stimuli into sets and the flexibility of response to changes in stimuli. Two artificial dimensions are used in the test: colour-filled shapes and white lines. The task requires participants to learn the applicable rule needed to select the correct icons. The test futures visual discrimination and attentional set formation, maintenance, shifting and flexibility of attention. It is primarily sensitive to fronto-striatal changes.[2829]

Multi-source interference task The Multi-source interference task (MSIT) requires subjects to identify which of a set of three numbers is different than its neighbors. Subjects must keep three fingers of their right hand positioned over response keys corresponding to the digits 1–3. In control (non-interference) trials, the target is in the same spatial position as its corresponding response key, and the flanking digits are not valid responses (i.e., they are 0s). In interference trials, the target is out-of-position relative to its corresponding key-press and is flanked by other viable targets.[30,31]

S.3.4.2. Verbal fluency

Verbal fluency test Verbal fluency requires goal-directed behaviors i.e. flexibility of thoughts, strategic planning, non-habitual responses and error-monitoring and has been suggested to reflect an aspect of cognitive flexibility i.e. the flexibility in shifting between categories.[12] The test requires the generation of as many words as possible within one minute. Both phonemic fluency (words starting with particular letters) and semantic fluency (animals, occupations) are tested. For test evaluation we used the sum of the subscores within each category.

There are different kinds of verbal fluency tasks, within the included studies the Word Fluency Task (WFT), the Lexical Verbal Fluency Test (LFT), and the Verbal Fluency Examination *(VFE).*

S.3.5. Phasia/ praxis

Boston Naming Test The Boston Naming Test (BNT) is a visual picture naming task in which 30 outline drawings of objects and animals are presented. The test is highly sensitive to identify naming deficits and impaired word-retrieve capacities in adults.

Token Test The Token Test (TT) is used for the assessment of auditory comprehension in patients with developmental and acquired disorders affecting language. Within this test, a participant needs to provide a gestural response (by pointing to or moving tokens) to a

verbal command provided by the examiner. The TT includes different kinds of tokens, varying in color, size, and shape. The test is divided into different sections and with every section the test becomes more difficult. Sections are based on length of the command, syntactic complexity, and working-memory demand.[32]

Manual/Motor Praxis Test The praxis test (MPT) is a less well-documented method to determine functional manifestations of dyspraxia.

S.3.6. Motor functioning

Finger-tapping test The Finger-Tapping Test (FTT) examines the motor functioning. It specifically examines motor speed and lateralized coordination. During administration of the test, the participant's handpalm is flat on the surface and the index finger is placed on a counting device. Participants are asked to tap the lever as quickly as possible within 10 second intervals. It traditionally includes five trials with a 5-point range for each hand. Bad performance on the FTT might indicate motor impairment or lateralized brain dysfunction.[33]

Purdue Pegboard The Purdue Pegboard (PP) test has been used most extensively in personnel selection for jobs that require fine and gross motor dexterity. The test measures the gross motor dexterity of hands, fingers and arms, as well as the fine motor dexterity of fingertips.[5]

S.3.7 Visuospatial perception/visuoconstruction

Visuospatial constructive test The visuospatial constructive test (VCT) or block-design test is a part of the WAIS. The test is used to examine a participants' visuospatial perception and is often assessed in children. It requires a participant to view a constructed model or a picture of a model and then recreate it with a provided number blocks, in a specified time limit. The difficulty of the block-design test varies with the number of blocks that is provided.[34]

Rey Complex Figure Test The Copy part of the Rey Complex figure test (RCFT), which assesses planning, organization and fine motor skills[5], can be used as a visuospatial construction test. The subject is as asked to draw a copy of the presented figure as accurately as possible.

S.3.8. Intelligence

Wechsler Adult Intelligence Scale The Wechsler Adult Intelligence Scale (WAIS) is a widely used measure for the establishment of cognitive functioning. The WAIS exists of various domains and focusses on either a single subtest or a number of indicators within the same domain, for interpretation of the test performance. Eventually scores can be contributed to either the verbal IQ or the performance IQ through assessment of the different included tasks.[35]

S.4 Individual outcome analyses

Simulation parameters

Patient	Amplitude	Pulse width (ms)	Frequency (Hz)
1	7.5 mA	90	110
2	5.5 V	90	130
3	5.5 mA	150	130
4	3.5 mA	90	130
5	7.0 mA	60	130
6	5.0 mA	90	130
7	8.2 V	60	130

	Y-BOCS (SD)	Boston Nt (SD)	Verbal fluency Semantic(Mean (SD)	Verbal fluency Phonetic Mean (SD)	Rey Auditory Verbal Learning test total Mean (SD)	Rey Auditory Verbal Learning test recall Mean (SD)	Trail making test A Mean (SD)	Trail making test B Mean (SD)	Trail making test ratio Mean (SD)	Stroop III – II Mean (SD)
Median, SD at baseline	33.86	26.75	43.71	32.29	54.29	12.0	42.0	92.39	2.43	32.37
	± 2.91	± 4.43	± 12.58	± 6.90	± 8.46	± 1.60	± 10.24	± 26.64	± 0.87	± 15.98
Patient 1	**-5.00**	-*	-3.00	**-9.00**	-1.00	1.00	-10.00	20.00	**2.68**	12.00
Patient 2	**-22.00**	3.00	1.00	**-8.00**	-8.00	**-2.00**	-1.00	-3.00	.01	2.00
Patient 3	**-15.00**	**-5.00**	4.00	**7.00**	**10.00**	0.00	2.66	9.39	.14	-12.01
Patient 4	**-16.00**	-1.00	**-15.00**	**21.00**	-7.00	-1.00	-4.52	2.72	.23	12.00
Patient 5	**3.00**	3.00	5.00	-4.00	**-14.00**	-1.00	-8.08	**31.32**	**1.55**	-.61
Patient 6	**-5.00**	1.50	-2.00	2.00	-7.00	0.00	**-11.23**	6.55	**.90**	-4.32
Patient 7	**-14.00**	.00	-12.00	-3.00	0.0	0.00	**-19.42**	0.14	**1.08**	-1.03

* Data unavailable. Individual change scores were defined as postoperative – baseline score. Differences exceeding > 1 SD of the baseline score are indicated in bold.

S5. Study outcomes per brain target

Target	Study	Times of measurement	Results[n]
VC/VS	Gabriëls, et al.+	2 (BL, M12)	*Memory*: RCFT(recall) improvement *Working memory*: ns *Executive functioning*: RSPM improvement *Cognitive flexibility*: ns *Verbal fluency*: ns *Visuospatial perception and construction*: ns
	Greenberg, et al.	2 (BL, M10)	*Domains unspecified – memory*: Recall improvement
	Goodman, et al.*	3 (BL, M6, M12)	*Memory: HVLT improvement in 1 patient Cognitive flexibility*: ns *Verbal fluency*: ToL mixed response *Motor system*: PP mixed respons
	Widge, et al.‡	2 (BL, n/a)	*Cognitive flexibility*: improvement
	Tyagi, et al.	2 (BL,W60)	*Cognitive flexibility*: ns
(am)STN	Mallet, et al ON-OFF؟	3 (BL, M3, M6)	*Memory*: ns *Working memory*: ns *Attention*: ns *Cognitive flexibility*: ns *Verbal fluency*: ns
	Mallet, et al OFF-ON؟	3 (BL, M3, M6)	*Memory*: ns *Working memory*: ns *Attention*: ns *Cognitive flexibility*: ns *Verbal fluency*: ns
(v)ALIC	Tyagi, et al.	2 (BL,W60)	*Cognitive flexibility*: IED improvement
/BNST	Aouizerate, et al¿	3 (BL, M1, M6)	*Memory*: BVRT improvement; FCSRT improvement *Executive functioning*: ns *Cognitive functioning*:WCST improvement;TMT-B improvemen
	Luyten, et al. ON	2 (BL, M2)	*Memory*: RCFT(recall) improvement; RAVLT: improvement *Executive functioning*: ns *Cognitive flexibility*: SWCT improvement;TMT-B improvement *Verbal fluency*: ns
	Luyten, et al. OFF	2 (BL, M2)	*Memory*: ns *Executive functioning*: ns *Cognitive flexibility*: ns *Verbal fluency*: ns
Nacc	Grassi, et al. Ψ	2 (BL, N/A)	*Executive functioning*: ns
(/NC)	Huff, et al.₽	2 (BL, M12)	*Attention*: CPT (Dprime N) improvement *Executive functioning*: ns *Verbal fluency*: ns
/ALIC	Mantione, et al.₹	3 (BL,W3, M8)	*Memory*: CVLT improvement *Working memory*: ns *Attention*; DSST improvement *Executive functioning*:ToL improvement; RAPM decline *Cognitive flexibility*: SCWT improvement;WCST (%perseverative errors) improvement *Verbal fluency*: semantic (occupations) improvement *Visuospatial perception and construction*: RCFT(copy) decline *Motor system*: ns
	Grant, et al.†	4 (BL,Y1,Y2,Y3)	*Executive functioning*: SSRT improvement *Cognitive flexibility*: IED improvement
	Barcia, et al.	2 (BL, M12)	*Memory*: ns *Working memory*: ns *Cognitive flexibility*:TMT-B improvement *Verbal fluency*: ns
ITP	Huys, et al.	2 (BL, M12)	*Executive functioning*: ns
	Jimenez et al.	6 (BL, M1, M3, M6, M9, M12)	*Memory*: ns *Cognitive flexibility*: ns Verbal fluency: ns *Motor system*: ns *Visuospatial perception and construction*: ns *Phasia/praxis*: ns

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Chapter 6

Effectiveness, timing and procedural aspects of cognitive behavioral therapy after deep brain stimulation for therapy-resistant obsessive compulsive disorder: a systematic review.

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Abstract

Background and aim: Deep brain stimulation (DBS) is an effective treatment for patients with severe therapy-resistant obsessive-compulsive disorder (OCD). 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. The aim of this review is to assess the efficacy, timing and procedural aspects of postoperative CBT in OCD patients treated with DBS.

Method

Systematic review of literature.

Results

The search yielded 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.

Conclusion

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 concomittant therapies to optimize treatment effects in OCD patients being treated with DBS.

Introduction

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder characterized by the presence of obsessions and/or compulsions. Its prevalence varies from 0.8 % up to 3% in the adult population [1]. The World Health Organization lists OCD as the 11th most common cause of secondary disability, accounting for 2.2% of the total years lived with disability [2]. Cognitive behavioral therapy (CBT), including exposure and response prevention (ERP), as well as pharmacotherapy with serotonergic medication, are the main forms of treatment for OCD. The effectiveness of CBT as treatment for OCD has been established in multiple studies [3,4]. However, its acceptability is limited: as much as 16% to 30% of patients offered CBT drops out during treatment [4,5]. Serotonergic medication, as well as augmentation with atypical antipsychotics, were shown to be effective, and the combination of medication and CBT is even more effective [6,7]. However, a large percentage of OCD patients show only a partial response or are refractory to psychotherapy and pharmacotherapy. In severe therapy-resistant cases, deep brain stimulation (DBS) may be an option. Although the target and stimulation characteristics may vary across studies and clinics, DBS is generally considered safe and effective for the treatment of therapy-resistant OCD [8]. DBS received approval as treatment for OCD by the European Comission (EC) in 2009, as well by the U.S. Food and Drug Administration (FDA) as a Humanitarian Device Exemption in the same year.

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 [9,10]. A more uniform and evidence-based approach may be beneficial for patients.

Up until now, the added effect of CBT to DBS for OCD has not been reviewed. The aim of this systematic review is to assess the literature on efficacy, timing and procedural aspects of postoperative CBT in patients being treated with DBS for therapy-resistant OCD, and to formulate clinical recommendations for future research and for offering CBT after DBS.

Methods

A systematic review of studies cataloged in PubMed was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (www.prisma-statement.org). The search was done over the full time span up until 17 April 2020. Only papers in English were included. We used the following broad Booleian search strategy: "(deep brain stimulation) AND (obsessive compulsive disorder) AND ((exposure and response prevention) OR (behavioral therapy) OR (cognitive behavioral therapy))". Given the limited yield of a narrower, exploratory search, all papers that addressed any form of postoperative CBT in patients receiving DBS for therapy-resistant OCD were included. This not only comprises clinical trials, cohort studies, case series and case studies, but also systematic and narrative reviews on DBS for OCD and position papers if they also comment on CBT after DBS. Reference lists of the included studies were checked for additional papers. The Evidence Project risk of bias tool was used as a means to assess the quality assessment of included studies (not being reviews) [11]. Two authors rated the quality (MG and AL) and discrepancies were resolved by consensus. Due to the very limited yield of our search, no minimum quality score was applied for inclusion. Effectiveness of CBT added to DBS was quantified by looking at the changes in scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) before and after CBT. Although the initial intention was to perform a meta-analysis, this was not possible because of the limited number of included studies that, in addition, used different indication criteria and different forms of CBT. Timing and procedural aspects of CBT in the studies are reported in a descriptive way.

Results

Literature search

The search yielded 181 papers. One additional paper was added after checking the reference lists of included papers [12]. Based on the title and/or abstract, 154 of these were excluded because of the following reasons: animal studies (n=14), not referring to OCD (n=61), not referring to DBS (n=15), not referring to CBT (n=28), not in English (n=10) and other reasons (including the absence of an abstract) (n=17). The remaining 28 papers were read in full. An additional 19 of these were excluded due to the following reasons: not referring to CBT (n=11), not referring to DBS (n=1) and other reasons (n=7). Eventually, 9 papers were included in the review: three randomized controlled trials (RCTs) [13-15], one cohort study [16], one case series [12], one qualitative study [17], one systematic review [18] and 2 narrative reviews [19,20]. These reviews were focused on the efficacy of DBS for OCD and not on the efficacy of CBT after DBS for OCD. Two of the included papers were based on the same RCT [13,14] (see Figure 1 for a PRISMA flowchart). The quality assessment of these studies are displayed in supplementary Table S1. The included systematic and narrative

reviews are not discussed in the 'results' section since they did not include other relevant papers than the ones discussed below.

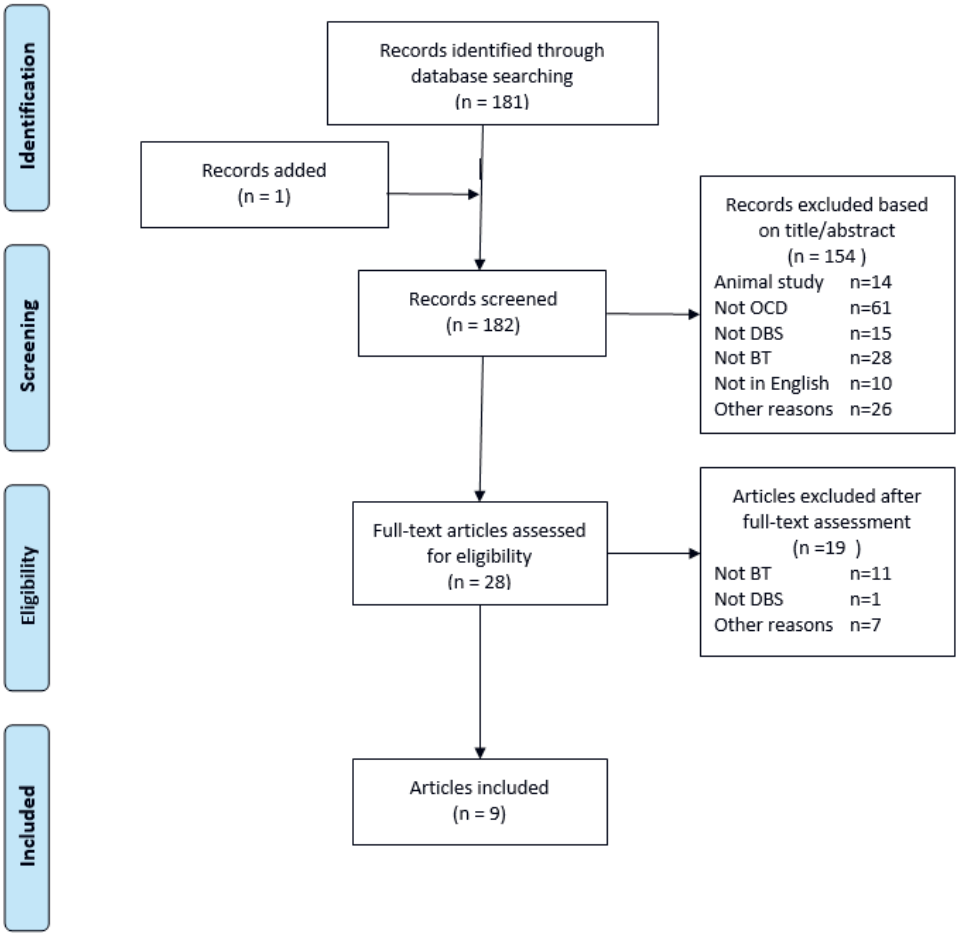

Figure 1. PRISMA flow diagramme. Abbreviations: OCD = obsessive compulsive disorder, DBS = deep brain stimulation, BT = behavioral therapy.

Description of included studies

The first RCT, by Denys et al. (2010) was a double-blind, shamcontrolled, clinical trial of DBS of the nucleus accumbens (NA) that included 16 therapy resistant OCD patients [13]. In this study, refractoriness was defined as no or insufficient response to treatment with at least 2 different selective serotonin reuptake inhibitors (SSRIs) at maximum dosage for at least 12 weeks, treatment with clomipramine hydrochloride for at least 12 weeks with adequacy of treatment established by plasma levels, one augmentation trial with an atypical antipsychotic for 8 weeks in combination with an selective serotonin reuptake inhibitor, and at least 16 sessions of CBT [13].

Design: The study had 3 sequential treatment phases: an initial open phase, starting immediately after electrode implantation and lasting for 8 months, in which stimulation parameters were optimized and CBT was started. DBS was administered per protocol, with restricted stimulation settings at 90μs, 130Hz and a maximum stimulation intensity of 5.0V. The effects of DBS were assessed with the Y-BOCS for obsessions and compulsions, with the Hamilton Anxiety Rating Scale (HAMA) for anxiety symptoms, and with the Hamilton Depression Scale (HAMD) for depression. After this open phase, a 1-month, double blind, sham-controlled phase started in which patients were randomly allocated to 2 periods of 2 weeks with the stimulators blindly turned 'on' (active stimulation) or 'off' (sham stimulation). CBT was continued throughout this phase. The double blind phase was followed by a 12-month maintenance phase in which the stimulator was turned on for all patients and settings adjusted as required. Patients were allowed to use psychopharmacological medication during the trial.

Effectiveness: Stimulation in the initial open phase resulted in a mean decrease of 46% in Y-BOCS score from 33.7 (baseline) to 18.0 points; a mean decrease of 52% on the HAMA score from 20.9 (baseline) to 10.1 points, and a mean decrease of 46% in HAMD scores from 19.5 (baseline) to 10.5 points. Without stimulation, the improvement gained with the addition of CBT disappeared rapidly, suggesting that efficacy of CBT depends on stimulation. In this double-blind phase, the mean difference in Y-BOCS score between the active and sham condition after correction for period effects was 8.3 (p=0.04). The mean difference in HAMA scores was 12.1 (p=0.1) and the difference in HAMD scores was 11.3 (p=0.01). It was reported that CBT was particularly effective in decreasing compulsions and avoidance behavior.

Mantione et al (2014) performed a secondary analysis of this same RCT that was aimed at quantifying the *added* treatment effect of CBT after DBS, as well as to discuss the methodology of the CBT programme used (see above) [11]. The average decrease on the Y-BOCS after optimization of stimulation settings was 25%. With the addition of 24 weeks of CBT to ongoing DBS treatment, there was an additional 22% decrease of total YBOCS score (p=0.021), without any additional effects on the HAMA or HAMD scores. The number of responders after CBT increased from 6 to 9 out of 16.

Timing: CBT was added when three conditions were fulfilled: an initial and substantial

decrease (on average 6 points) in Y-BOCS score had to be obtained, there had to be no further decrease in Y-BOCS during three consecutive visits (which was usually after 8 weeks of stimulation), and it had to be observed that patients avoided resisting their compulsions or avoided anxiety-provoking exposure situations.

Procedural aspects: The CBT program consisted of 24 weekly individual face-to-face sessions of 60 minutes each. The protocolized treatment started with an extensive evaluation of the patient's motivation. Once motivation was established, therapy started with ERP and gradually introduced more cognitive elements at later stages [14,21].

Tyaghi et al (2019) performed a randomized, double blind counterbalanced comparison of DBS of the anteromedian subthalamic nucleus (STN) and ventral capsule/ventral striatal (VC/VS) stimulation in 6 patients [12]. In this study, treatment resistance was defined as no sustained benefit from treatment with at least two SSRIs for a minimum of 12 weeks at optimal doses, augmentation of SSRI treatment with an antipsychotic or extension of the SSRI dose beyond recommended limits, and at least two trials of CBT with a minimum of 10 sessions, of which one as inpatient.

Design: the study consisted of two phases: an initial randomized phase of 12 weeks with stimulation of either the STN or the VC/VS, followed by an open phase in which both targets were stimulated. Stimulation was started after a mapping session at 60μs and 130Hz, without restrictions for stimulation intensity and also allowing stimulation of different contact points, both monopolar and bipolar. Next, there were two additional 12-week open phases: in the first one stimulation settings were optimized using data from previous phases. In the second phase, CBT was added to optimized DBS using the combined VC/VS and STN targets.

Effectiveness: Psychopharmacological treatment was allowed and kept constant during the trial. Overall, the score on the Y-BOCS reduced by 60%, from 36.2 at baseline to 14.3 when optimal stimulation settings were administered. Adding a in-patient CBT resulted in an additional decline of the Y-BOCS score by 35% to 9.3 ($p=0.09$; total decline from baseline 74%). Although obsessions and compulsions improved significantly from baseline to optimal stimulation, there was no *statistically* significant added improvement after CBT. Scores on the Montgomery-Asberg Depression Rating Scale (MADRS) declined from 28 at baseline to 13 during optimal stimulation settings and further reduced to 7 after CBT (information from the authors). The authors conclude that there is no further improvement in obsessions and compulsions due to CBT after optimal stimulation settings, and that this reflects a floor effect of DBS on OCD. With 'floor effect' they intend to say that no further improvement of OCD symptoms would be possible after optimization of stimulation settings.

Timing: CBT was started standard after 24 weeks

Procedural aspects: CBT, including exposure and response prevention, was applied in an inpatient unit while optimal stimulation settings were maintained.

Greenberg et al (2006) report on the long-term (> 3 years) follow-up of 10 therapy-resistant OCD patients being treated with VC/VS DBS [16].

Effectiveness: The average Y-BOCS score declined by 35% from 34.6 preoperatively to 22.3 after three years of DBS. All pharmacotherapy was allowed, but kept constant up to three

months after the start of DBS treatment. The information provided in the paper does not allow to calculate the added effect of behaviour therapy to DBS on OCD symptoms. Clinically, the authors describe a 'notably enhanced motivation to engage in goal directed activities' during DBS, which also included enhanced motivation for CBT, which all patients had attempted unsuccessfully before the procedure. They consider that this increased motivation may have been a key factor in the patients' clinical progress.
Timing: If patients had had behaviour therapy immediately prior to DBS, this was allowed to continue after the start of DBS; new behaviour therapy was allowed to start only six months after the start of DBS. No details on the number of patients that received behavioural therapy postoperatively is given, nor details about the type, frequency, duration and way of delivery of the behavioural therapy.
Procedural aspects: There is no information on procedural aspects.
Abelson et al (2005) report a case series of 4 therapy resistant OCD patients being treated with DBS of the anterior limb of the internal capsula, with the tip of the electrode adjacent to the nucleus accumbens [12]. After operation, a 12-week double-blind testing stage was followed by an open-ended, open stimulation phase, with efforts to optimize results by adjusting stimulation settings and by pharmacotherapy and CBT. No further details on the effectiveness, timing and procedural aspects of CBT is given.
The qualitative study by van Westen et al (2019) reports on the results of interviews with 8 professionals involved in DBS treatment of OCD patients, as well as experiences from embedded patient observation of the author [17]. These professionals identified the process in which patients become increasingly engaged in their process of improvement as an important predictor of effect. As the patient changes, new possibilities emerge, one of which is renewed treatment with CBT, to reduce remaining symptoms and expand healthy behavioral repertoires [17].

Discussion

Whereas it is a common practice to offer patients with therapy-resistant OCD treated with DBS a course of CBT after their operation, its effectiveness, timing and procedural aspects, such as the preferred way of delivery of such therapy, has hardly been studied. In spite of the fact that the importance of post-operative CBT is stressed by various authors [18-20], only two trials have specifically focussed on CBT added to DBS [13-15].

Effectiveness

The two studies that assessed the effects of CBT added on to DBS both support its effectiveness. In the study by Denys et al, CBT was responsible for significant additional reduction of 22% on the Y-BOCS after optimal stimulation settings were achieved [14]. In the study by Tyagi et al, there was a trend for an additional improvement of 35% on the Y-BOCS (P = 0.09). Whereas this may not be *statistically* significant, there is a clear trend towards significance for this finding and it constitutes a clinically relevant change. In our opinion the lack of a statistical significance may well be due to a power problem because of the very low number of included patients (n=6). So contrary to the authors, who present this as a negative outcome, we consider this study in support of postoperative CBT.
In theory, the effectiveness of CBT may also depend on the preoperative cognitive state of the patient, as well as on the potential cognitive side effects of DBS. Whereas in patients with Parkinson's disease, cognitive side effects of DBS - especially of the subthalamic nucleus - has been associated with reduced processing speed and working memory [22], there is little evidence of any detrimental effect of DBS - of any target - on the cognitive performance of OCD patients [23]. Studies that do report on neuropsychological measures report no relevant change in cognitive performance after DBS [24], and in one case even an improvement in cognitive flexibility for STN DBS but not for VC/VS DBS [15]. None of the included papers report on problems administering CBT due to cognitive side effects.
There has been some discussion on whether the effects of CBT may depend on the DBS target. Mantione et al. suggest that the effect of CBT in their study may be specific to the NA target of stimulation, since NA DBS has a profound effect on anxiety and depression, as opposed to e.g. DBS of the STN, which reduces compulsions without significant effects on mood and anxiety [11]. However, in the study by Tyagi, the additional improvement in patients with STN and VC/VS DBS is in the same range, if not larger than in the study by Mantione [15]. Based on these scarce data, we expect CBT to be effective as add-on treatment to DBS in therapy-resistant OCD patients, irrespective of the stimulation target. However, only further studies comparing the effectiveness of CBT in OCD patients with different DBS stimulation targets can reveal a potential target related effect of CBT.

Timing

The same two studies used different criteria for starting CBT. Denys et al, started CBT after partial response, defined as a substantial reduction of on average 6 points on the Y-BOCS, without further decrease during three consecutive visits [13,14]. In the study by Tyagi, CBT was started after 36 weeks in every patient, irrespective of the amount of improvement achieved by DBS [15]. In clinical practice the question of when to best start CBT is an important one. It does not seem sensible to start CBT immediately postoperatively after electrode implantation and activating the DBS system. The mental state of the patient has

not changed yet, and because of that there is no reason to expect that treatments that were ineffective before DBS would now be effective. It also makes no sense to start CBT if the response to DBS is very large, since there may not be any relevant treatment goals left to work towards. The best time to start CBT is probably when there is a partial response to DBS. The altered mental state of the patient, with not only some reduction in obsessive-compulsive behavior, but usually also reduced anxiety and improved mood, provides a different starting position for CBT, and the patient may be more able and motivated to comply with therapy, as was also described by Greenberg et al, and by Van Westen et al. in their qualitative study [16,17]. The question then is *when* to start CBT in case of partial response. Some clinicians routinely start after a certain period (e.g. after 8 or 12 weeks). Other clinicians start CBT when it is assumed that optimal stimulation settings have been achieved. Whereas this may be preferable in a research context, in order to separate the differential contribution of DBS and CBT to the response, clinically this is debatable. On one hand, reaching optimal stimulation settings may take a long time in many patients, which would lead to an unacceptable delay for therapy and loss of momentum; on the other hand, these patients have already experienced non-effective CBT and it is important to spare them another failure because of starting CBT to soon, as this would decrease their motivation for another attempt when stimulation parameters are optimal. One option is to assess the 'readiness' for CBT, as mentioned above. Another option may be to look for improvement of cognitive measures that may increase the likelihood of successful CBT. A recent intervention study showed that the effect of VC/VS DBS is explained in part by enhancement of cognitive control by the prefrontal cortex. In this study, DBS improved the patients' performance on a cognitive control task and increases theta (5–8Hz) oscillations in both medial and lateral PFC, which predicts the clinical outcome [25]. Perhaps such indicators could be made to clinical use and help to indicate the best time to start CBT after DBS.

Procedural aspects

In the study by Denys et al, CBT/ERP consisted of 24 weekly individual face-to-face sessions of 60 minutes each, administered on an outpatient basis. Tyagi et al. provided CBT/ERP for 12 weeks on an in-patient basis in a neuropsychiatry unit. In both studies, the therapy was provided by the DBS clinic. This may be feasible in a research setting, but in routine clinical practice this will be more difficult to ask from patients once the DBS settings are optimized, given the distance that many of them will have to travel to the DBS clinic. Because of this, therapy is often organized in the region where the patients live. However, whereas many behavioral therapists from local/regional psychiatric services may have experience in treating OCD patients, few will have experience treating OCD patients with DBS. In-patient treatment is one option to let patients benefit from the expertise of therapists of the DBS clinic, but this will be costly and may not be more effective than out-patient treatment.

Another way of letting patients benefit from therapists with DBS experience is to explore novel ways of administering therapy, such as by telephone, videoconferencing or online.
In addition, other indications for CBT in the peri-operative period should also be considered. CBT could be administered with different objectives and if necessary, a different procedural approach. It could for instance already be started pre-operatively with the intent to enhance motivation for change post-operatively. Such pre-operative intervention has not been studied yet. Also, the content of the cognitive aspects of therapy could be adapted to address some issues specific to DBS, such as specific psychoeducational purposes related to DBS and preoccupation with stimulation settings. Moreover, after substantial improvement, low frequency long term continuation therapy may be helpful in preventing relapse.

Synthesis and recommendations

Only two studies specifically address postoperative CBT. These used different stimulation targets and stimulation protocols, as well as different approaches to administering the therapy. Both studies suffer from a number of limitations, most importantly a small sample size, and the lack of a control condition for the CBT. In addition, the focus is strongly on obsessive and compulsive symptoms, whereas a focus on quality of life and general (social) functioning may be more important to the patient [26]. The other included studies mention postoperative CBT, but do not provide any details on effectiveness, timing and procedure.
DBS is not a stand-alone treatment for therapy-resistant OCD. After their operation, many patients continue to take medication for OCD, and/or receive some form of psychotherapy to deal with remaining symptoms or problems adjusting to the new situation. The overall treatment effect is the resultant of the DBS plus adjunctive therapies, and studies into the effectiveness of DBS should also take these concurrent treatments into account.
From a clinical point of view, there is a need for an evidence based algorithm for applying concomittant therapies, both psychotherapy as well as pharmacotherapy. As far as psychotherapy is concerned, there should be clear criteria as to when to start psychotherapy and the module should be adjusted to patients being treated with DBS. In our opinion, CBT should be started after a predefined level of clinical repsonse to DBS, which is open for dicussion, and the CBT module should address issues specific to DBS patients such as a changed personal identity due to being dependent on a device for symptom control and well-being, preoccupation with stimulation settings, and adjusting to the new situation with gained time because due to obsessions and compulsions after a long time of therapy-resistance and severe obsessive-compulsive behaviors that rendered typical family life, social contacts or employments unfeasible [27]. In order to let patients benefit from the experience of CBT therapists working in DBS clinics, other ways of administering CBT such as by telephone, videoconferencing or online, should also be developed and evaluated.
From a research point of view, future studies into the efficacy of DBS for OCD should follow a design that also allows the evaluation of the added effect of these concurrent treatments,

and helps determining the place of these concurrent treatments in a treatment algorithm of OCD patients after DBS. This implies that there should be a control condition for CBT in order to assess the placebo response of CBT treatment. It also implies that sample size should be large enough to allow evaluation of the added treatment effects of CBT. Since it is unlikely that the required sample sizes will be achieved within a reasonable amount of time in a single DBS center, multicenter studies should be initiated. It is essential that collaborating centers not only protocolize their CBT treatment, but also that they align their clinical practice with respect to DBS with respect to stimulation target, strategies to optimalize stimulation parameters and follow-up assessments. This would require a closer collaboration between DBS clinics on both a national and international level.

Conclusion

Preliminary findings show that postoperative CBT is effective as add-on treatment to DBS in patients with therapy-resistent OCD. Further studies are necessary to establish the place of CBT after DBS. These studies should have larger sample sizes and designs that are adequate to quantify the added effects of both CBT as well as pharmacotherapy. In order to let patients benefit optimally from the experience and expertise of behavioral therapists working in DBS clinics, novel ways of administering CBT, such as administered by telephone, videoconferencing or online, should also be studied.

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Chapter 7

Surgical and Hardware Related Adverse Events of Deep Brain Stimulation: a 10-year single centre experience.

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Abstract

Introduction

Although Deep Brain Stimulation (DBS) has proven effective, surgical and hardware related Adverse Events (AEs) occur that may impact upon the quality of life. The aim of the present study was to give an overview of the nature and frequency of those events in our centre and to describe the way they were dealt with. Furthermore, an attempt was made at identifying risk factors in order to inform possible future preventive measures.

Methods

Patients undergoing DBS related procedures between January 2011 and July 2020 were retrospectively analyzed to inventorize AEs. 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.

Results

From January 2011 to July 2020, 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*. 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) (9.95%, 20/201) and wire tethering (2.49%, 5/201) followed by hardware failure (1.99%, 4/201), skin erosion (1.0% 2/201), pain (0.5%, 1/201) lead migration (0.52%, 2/386 electrode sites) and hematoma (0.52%, 2/386 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.

Conclusion

Major AEs involving intracranial surgery related AEs or AEs requiring surgical removal or revision of hardware are rare. 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.

Introduction

Deep Brain Stimulation (DBS) is nowadays an established and widely applied treatment for several brain disorders, such as Parkinson's disease (PD), tremor, epilepsy, and Obsessive Compulsive Disorder (OCD).[1–4] Although this neurosurgical treatment has shown to be effective on the short and long term, some patients may not experience an improvement of their quality of life due to undesired stimulation induced side effects, or adverse events (AEs).[5–8] The reported incidence of surgical and hardware related AEs varies largely.[9] In a systematic analysis including 96 articles, the incidence of a variety of AEs related to the hardware, including surgical site infections (SSI, 5.12% [4.45-11.51]), lead migration (1.6% [0.72-3.04]), fracture or failure of the lead or other parts of the implant (1.46% [0.41-4,2]) and skin erosions without infection (0.48% [0.36-7.14]) were reported.[9] Interestingly, indications such as Tourette's Syndrome (TS) and epilepsy were found to be more prone to undergo hardware related SSIs when compared to (PD).[9,10] However, patient or surgery related factors associated with, and management of, surgical and hardware related AEs of DBS are not frequently described.[11–14]

In light of increased application of DBS in established indications, as well as emerging new indications and substantial resources required for DBS (i.e. extensive programming, life-long follow-up and recurrent hardware costs) reporting current surgical and hardware related AEs essential for evaluating the risk-benefit ratio of this therapy. Here, we present a comprehensive analysis of the AEs occurring following DBS associated surgical procedures over a period of 10 years of a single centre. Aim of the present study was to give an overview of the nature and frequency of those AE's in our centre and to describe the way there were dealt with. Further, an attempt was made at identifying possible risk factors in order to inform possible future preventive measures.

Methods

Data assessment and follow-up

This study involved a retrospective chart review of a single academic center (Maastricht University Medical Center) of all patients receiving a DBS system or IPG replacement between January 2011 and July 2020. Data was retrieved from chart records and included age, sex, diagnosis and the presence of co-morbidity. Details of the surgical sessions were documented, including the length of procedure and, if applicable, the time to internalization of external leads. All peri- and post-operative AEs related to DBS were recorded including hematoma, pain, SSI, wound dehiscence, skin erosion, painful extension wire tethering and migration or fracture of brain electrodes or extension wires. In addition to the demographic data, we documented several risk factors supposedly predisposing for DBS hardware related AEs: surgical procedure duration, surgical experience, Body Mass Index (BMI), smoking, diabetes and post-operative wound leakage. Only patients with a minimum follow-up of 6 months were included, resulting in a mean follow-up time of 43 ± 31 months.

Ethical statement

The work described was conducted in accordance with the Declaration of Helsinki. Approval by an institutional review board and patient consent is not required by law in case of research with patient data collected in the course of routine clinical care if the data are made anonymous and non-identifiable (see the website of the Dutch Central Committee for Research with Humans: https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/your-research-is-it-subject-to-the-wmo-or-not).

Surgical procedure

Deep Brain Stimulation implantation

For a detailed description of our stereotactic DBS procedures, see also previous publications.[15–18] In short, surgical procedures were performed under general anesthesia with remifentanil and propofol (n=56) or under local and procedural sedation and analgesia (PSA with application of 1% lidocaine with epinephrine 1:100 000 at the scalp incision and pin sides(n=145).[19] The total of 201 DBS implantations were performed by four surgeons 1 (n=74), 2 (n=41), 3 (n=71) and 4 (n=14). However, all surgeons had multiple years of experience before the defined period. A Leksell stereotactic frame (Model G, Elekta Instrument Stockholm, Sweden) was mounted on the skull and a peri-operative CT-scan of the head with frame was acquired and fused with the pre-operative MR images using

Framelink software (Medtronic, Fridley, USA) or Brainlab iPlan (Brainlab, Feldkirchen, Germany). The planned target was defined in relation with the anterior and posterior commissures and adjusted based on the patient's individual anatomy. Typically, the angles of approach were chosen in order to avoid the lateral ventricle and the caudate nucleus. In 194 patients micro-electrode recordings (MER) were performed. The techniques for lead placement were the same for both staged and single-staged implantations. For single staged implantations, the stereotactic frame was removed after both frontal incisions had been closed. In case of local anesthesia, the patient was placed under general endotracheal anesthesia for implantation of the lead extensions which were subsequently connected to an Internal Pulse Generator (IPG) infraclavicularly or abdominally. Where an abdominal location of the IPG is preferred, in order to reduce tethering complaints and increase the distance with the brain electrode in case of SSI. For two-stage implantation procedures, fixated electrodes were connected to an externalized extension cable, where after a mean of 5 days the electrodes were internalized.

Internal Pulse Generator (IPG) replacement

Internal Pulse Generator replacement surgeries were routinely performed under local anesthesia (1% lidocaine with epinephrine 1:100 000) by a stereotactic and functional neurosurgeon. As for primary DBS implantation, surgeries were generally postponed if there was any relative contra-indication to proceeding (i.e. recent illness). Skin preparation was performed with a chlorhexidine solution (chlorhexidine digluconate 0.5% in alcohol 70%) or povidone-iodine. After disinfection, the surgical site was covered with an iodine impregnated adhesive (Ioban, 3M, St Paul, USA), when iodine intolerance was absent. Implants were opened only right before insertion. Wound closure was typically in multiple layers to prevent from dead space formation.

Perioperative Sterile Techniques/ Antibiotic prophylaxis

Complete hair removal was abandoned in 2014.[20] Henceforth, for both single- and two-stage implantation procedures, the evening before lead placement hair was washed with povidon-iodine shampoo. Perioperative sterile techniques have been described previously.[20] Prophylactic antibiotics were given to patients in single- and two-stage implantation procedures. Patients received 2 gram of cefazolin one hour to 30 minutes pre-operatively, and subsequently 1 gram every 4 hours followed by 1 gram every 6 hours. Patients with penicillin or cephalosporin allergies typically received vancomycin (single 1000mg dose). In addition, the cement which was used for fixation of the leads contained tobramycin or erythromycin (Stryker, Kalamazoo, MI, USA). Prior to IPG replacement, patients received a single dose of IV antibiotics. Proceeding skin closure during both IPG replacement and

primary the surgical site was injected with several milliliters of a 20mg/ml gentamicin solution, no vancomycin powder was instilled.

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics, version 20 (IBM Corp., Armonk, N.Y., USA). For categorical variables, we used the chi-square test to compare proportions between groups. The odds ratio and p value for each comparison were computed when appropriate. To investigate the predictive power of co-morbidity (see above) and predictability of postoperative parameters, we either used univariate or binary regression analyses. The level of significance was accepted at $p<0.05$ and Bonferroni corrected where appropriate. Unless otherwise indicated, results will be displayed as a mean ± SD.

Results

Demographics

DBS implantation procedures

From January 2011 to July 2020 a total 386 leads were implanted in 200 consecutive patients, within 201 procedures. Patients were finally implanted with bilateral (n=185) or unilateral (n=16) electrodes from various models; Model 3387 (n=45), Model 3389 (n=146) (Medtronic, Fridley, USA), Abbot Infinity (n=10) (Abbott, Illinois, USA) which were fixed in the burr hole, with acrylic cement (n=172) (Antibiotic Simplex; Stryker, Kalamazoo, MI, USA) or with a device Stimloc (n=22) (Medtronic, Fridley, USA) or Guardian (n=7) (Abbott, Illinois, USA). The procedure was staged in 38 (19%).
IPGs used for implantation were the Activa PC (n=177) RC (n=4) SC (n=10) (Medtronic, Fridley, USA) or Infinity (n=10) (Abbott, Illinois, USA). IPGs were implanted in the infraclavicular region or in the abdominal wall in 31 and 170 cases respectively.
The diagnosis included PD (n=103), epilepsy (n=35), essential tremor (ET, n=25), dystonia (n=15), OCD (n=13), TS (N=8) and pain (n=1). Age at time of surgery was 54 ± 16 years ranging from 10 to 88 years. The mean follow-up time after surgery was 40 ± 29 months. See table 1 for patient characteristics of primary implantations.

	N (%)	*Non- staged (%)*	*Mean ± SD*	*Female (%)*	*Bilateral (%)*	*STN*	*VC/VS*	*Vim/ PSA*	*ANT*	*GPi*	*GPe*	*VP*
PD	104 (52)	87 (84)	61 ± 8	33 (32)	98 (94)	90	0	9	0	5	0	0
Epilepsy	35 (18)	24 (69)	39 ± 12	12 (34)	35 (100)	0	0	0	35		0	0
ET	25 (12)	19 (76)	65 ± 13	8 (32)	17 (68)	0	0	25	0		0	0
Dystonia	15 (7)	15 (100)	37 ± 23	6 (40)	14 (93)	0	0	0	0	14	1	0
OCD	13 (6)	12 (92)	42 ± 12	8 (62)	13 (100)	0	13	0	0		0	0
TS	8 (4)	4 (50)	29 ± 10	3 (38)	8 (100)	0	0	0	0	8	0	0
Pain	1 (1)	0 (*)	79	0(*)	0 (0*)	0	0	0	0		0	1
Total	201	161 (81)	54 ± 16	70 (35)	185 (92)	90	13	34	35	27	1	1

Table 1: Patient characteristics of DBS implantations. PD: Parkinson's disease, ET: essential tremor, OCD: obsessive compulsive Disorder STN: subthalamic nucleus, VC/VS: ventral capsule/ ventral striatum, Vim/PSA: thalamic ventral intermediate nucleus /posterior subthalamic area, ANT: anterior nucleus of the thalamus, GPi: globus pallidus internus, GPe: globus pallidus externus, VP: ventral pallidum. * One male patient received a unilateral electrode in a staged procedure.

	IPG replacements	**Age**	**Sex**	**Replacements/ stimulation year**
	N (%)	Mean ± SD	*Female (%)*	Mean ± SD*
PD	160(52)	68 ± 8.1	31 (19)	0.5±0.4
Epilepsy	8 (3)	39 ± 5.7	3 (38)	0.3±0.1
ET	58 (19)	67 ± 13	12 (21)	0.4±0.2
Dystonia	8 (3)	52 ± 24	2 (25)	1.5±1.1
OCD	13 (4)	49 ± 9	5 (38)	0.8±0.2
TS	58 (19)	44 ± 12	2 (3)	0.8±0.1
Pain	0	/	/	/
Total	305	61 ± 15	55 (18)	0.5± 0.4

Table 2: Patient characteristics of IPG replacements. IPG: implantable pulse generator, N(%): number of IPG placements per indication and its percentage as part of the PD: Parkinson's disease, ET: essential tremor, OCD: obsessive compulsive Disorder STN: subthalamic nucleus , VC/VS: ventral capsule/ventral striatum, Vim/PSA: thalamic ventral intermediate nucleus /posterior subthalamic area, ANT: anterior nucleus of the thalamus, GPi: globus pallidus internus, GPe: globus pallidus externus, VP: ventral pallidum * IPG replacements / stimulation year was calculated for the cohort receiving brain electrodes in the period between January 2011 to July 2020.

Implantable Pulse Generator replacements

Over the period of January 2011 to July 2020, 307 IPG replacements were performed in 142 unique patients. Two patients were excluded from further analyses as brain electrodes were not implanted in our own center. To note, the remaining 140 included 60 patients with primary lead implantations before January 2011. Of the remaining 82 patients who received brain electrodes in the defined period, the mean time to first IPG replacement was 1195 ± 506 days and the mean IPG replacement per stimulation year was 0.5 ± 0.4 (table 2), with no difference between indications.

Revision surgery

Additional surgery for AEs or therapy revision was performed in 38 patients of which 37 received brain electrodes in the defined period. Revision procedures could be categorized into surgery related to SSI (31 procedures in 20 patients), wire tethering (n=5), skin erosion or wound dehiscence (n=4), hardware failure (n=5), loss of treatment benefit or stimulation related AEs (n=6), perioperative defects (n=2), reimplantation or reinternalization (n=10), abdominal hematomas (n=1), and revision after lead (n=2) or IPG (n=4) migration or malposition.

Adverse Events

Overall, there were 57 AEs in 52 individuals; including 40 AEs in 40 patients occurring in the cohort receiving brain electrodes in the period of January 2011 to July 2020. Table 3 summarizes the number and nature of the hardware related AEs after implantation. The number of AEs after IPG replacement are summarized in table 4.

Peri-operative damage

Peri-operative damage of the DBS lead was observed in one patient (1/386 electrode sites = 0.26%). In this case, the distal contact point of one brain electrode was broken, which was observed before internalization in a staged procedure. Per-operative damage of the extension cable occurred during IPG replacement in one patient. (1/305 IPG replacement procedures = 0.33%) The damaged hardware was revised immediately in both patients.

Lead migration

Routine imaging typically obtained several days postoperatively revealed lead migration in two patients (2/386 electrode sites = 0.52%) requiring immediate surgical revision of the electrode.

Implantable Pulse Generator dislocation

Four patients reported (4/508 total procedures = 0.79%) a dislocated IPG, of which two patients following initial implantation. Apart from one patient that was treated conservatively, all IPG dislocations required repositioning.

Hematomas

Two patients (2/386 electrode sites = 0.52%) developed a subdural hematoma (SDH) post-operatively. In one patient a SDH was observed following an in-hospital fall and another patient developed a symptomatic SDH several weeks after DBS implantation, corresponding to the location of direct post DBS implantation pneumocephalus. Both patients required surgical drainage of the SDH. Four patients developed a hemorrhage of the IPG pocket following IPG replacement (3/305 IPG replacement procedures = 0.98%) or initial implantation of the hardware (1/201 initial implantations of the stimulation system = 0.50%). Three patients were treated conservatively with prophylactic antibiotics, one patient required surgical revision considering a significant normocytic anemia.

Wire tethering

Extension cable tethering occurred in eight patients. Typically, patients had complaints of retro-auricular 'bowstringing' (3) or pain around the IPG location (5). For the latter there was an equal distribution between an abdominal or infraclavicular location (3 vs. 2). Five patients developed complaints following after initial implantation (5/201 implantation procedures = 2.49%), while three patients presented with complaints after IPG replacement (3/305 IPG replacement procedures = 0.98%). In three patients, conservative management i.e. push-up bra for or tight undershirt provided significant relief of the complaints. The remaining patients underwent successful surgical revision.

Hardware failure

After a mean of 18 months, four patients underwent revision surgery because of hardware failure (4/201 implantation procedures = 1.99%) as manifested by high impedances (3) or intermittent stimulation (1) and concomitant recurrent disease symptoms, requiring replacement of the relevant hardware. In one patient the hardware failure debuted after trauma, although no hardware disconnection was found. In the remaining patients the cause of malfunction could not be identified. There was no difference in the occurrence of hardware failure between manufacturer ($p= 0.107$) or DBS indication ($p = 0.633$).

Pain

Two patients reported an excessive sensation of pain after surgery. One patient (1/386 electrode sites = 0.26%) had complaints of occipital neuralgia with the maximal point just cranial to the connection of the brain electrode to the extension cable, one year after surgery. After ruling out structural causes or lead displacement by MRI, the patient was treated with corticosteroid injection with good result. A second patient had complaints of persisting wound pain developing after multiple (+10) IPG replacements due to high constant voltage stimulation settings (1/305 IPG replacement procedures = 0.33%). Fortunately, complaints resolved after conservative treatment and the IPG was replaced by a rechargeable system.

Wound dehiscence

Wound dehiscence, defined as any separation of approximated wound edges without any signs of infection, was observed in one patient following IPG replacement (1/305 IPG replacement procedures = 0.33%). The wound was closed with secondary intention and prophylactic antibiotics.

Skin erosion without infection

Skin erosion of the IPG pocket (1) and cranial electrodes (2) was observed in three patients following initial implantation of the hardware (2/201 implantation procedures = 1.00%). One incident of skin erosion was documented after replacement of the IPG (1/305 IPG replacement procedures = 0.33%). For management, one case of light erosion was treated conservatively without antibiotics. All other incidences of skin erosion were surgically revised with additional prophylactic antibiotic therapy.

Surgical site infection

SSI was the most common reported surgery related AE. In the period from January 2011 to July 2020, 20 infections occurred after primary implantation of DBS hardware (20/201 implantation procedures= 9.95%). There was no difference in SSI incidence in non-staged vs. staged procedures (11% vs 5.0%, p=0.256) or between different indications (Table 3). Further, no difference in SSI incidence was observed before and after April 2014, when complete hair removal was abandoned (7% vs 11%, p=0.38). The median time interval between operation and SSI was 85.9 days (range: 4-247). Following primary DBS implantation, SSI occurred most frequently at the IPG site and there was no difference between an infraclavicular (n=2) or an abdominal (n=8) location (p = 0.694). In three patients the SSI involved multiple sites i.e. retro-auricular and abdominal. The most frequent pathogen was Staphylococcus aureus (31%).

Four PD patients and one TS patient developed an SSI following IPG replacement located infraclavicular (4) or abdominal (1), (5/305 IPG replacement procedures = 1.64%). The median interval between IPG replacement and SSI occurrence was 73 days (range: 18-178), with 80% of the SSIs occurring within three months.
25 patients presenting with a SSI were treated according to several treatment strategies (Table 5). Patients were initially treated with IV antibiotics.(n=14), in combination with wound revision (n=7) or direct partial removal of the hardware (n=4). In none of the cases patients' hardware was removed completely at the beginning of treatment. Patients who developed an SSI early after initial implantation/IPG replacement were more likely to receive IV antibiotics alone. Of the patients treated with antibiotics alone, 13 patients developed an SSI following initial implantation. In six patients (42.9%) this treatment with IV antibiotics was successful, with an antibiotic regime aimed at the causative pathogen for six weeks IV in ambulatory care followed by six weeks oral antibiotics. The majority of the patients received flucloxacillin, with a mean follow up of 18±10 months. Of the remaining eight patients that required additional removal of hardware. Of these, 6 cultures positive for S. aureus. In none of the three patients with a multiple site SSI (scalp and IPG site) treatment with IV antibiotics was successful. Four patients received initial partial removal of the hardware, comprising only the IPG (1) or removal of both the IPG and extension leads (3), which was successful in 75%. One of the patients receiving removal of both IPG and extension leads, required complete removal of the hardware eventually. An SSI re-occurred after partial removal of DBS hardware and subsequent re-implantation after 43 and 214 days respectively in two patients necessitating complete removal. When initial treatment was unsuccessful, the mean time to secondary treatment (partial or complete removal) was 64 days for the group that initially received antibiotics, 49 days for the wound revision group and 499 days for partial removal.

Surgical features and risk of Adverse Events

There were no differences between the incidence of total AEs and surgical features (table 6), or surgeon (p=0.15). For SSI and wire tethering, we further analysed specific surgical features known for or more likely to cause these AEs. For staged and non-staged procedures, there was no difference in incidence of SSI 11% (18/161) vs. 5% (2/40) at p= 0.91. There was also no difference in SSI requiring (partial) removal of hardware following postoperative externalization of the DBS electrodes 50% (9/18) vs. 50% (1/2), p = 1.00. Likewise, we did not identify a difference of SSI occurrence after fixation of the DBS electrodes with antibiotic impregnated acrylic cement or with a device (e.g. Stimloc) 11% (3/28 vs 11% (17/173), p = 0.99. SSI was more common in rechargeable vs non- rechargeable IPG's (50% (2/4), p= 0.007). Nevertheless, this result was non-significant after correction for multiple testing (0.05/9). Considering complaints of wire tethering, no difference was observed for an infraclavicular 3% 1/31 or abdominal 2% (4/170) location of the IPG.

Risk factors

A binary regression analyses was performed to identify risk factors for wire tethering and SSI following initial implantation of the hardware. None of the potential risk factors were significantly associated with these AEs. Infection risk on a per-patient basis was not predicted by age, indication, gender, diabetes mellitus, obesity, use of anticoagulation, and smoking.

	N	Total no. of AEs (%)	SSI	Skin erosion	Wound dehiscence	Wire tethering	Peri-operative damage	Hematomas	Hardware migration	Hardware failure	Pain
PD	104	22 (21)	10	1	0	5	1	2	1	1	1
Epilepsy	35	7 (20)	2	1	0	0	0	0	2	2	0
ET	25	6 (24)	4	0	0	0	0	1	0	1	0
Dystonia	15	5 (33)	4	0	0	0	0	0	1	0	0
OCD	13	0 (0)	0	0	0	0	0	0	0	0	0
TS	8	0 (0)	0	0	0	0	0	0	0	0	0
Pain	1	0 (0)	0	0	0	0	0	0	0	0	0
Total	201	40 (20)	20	2	0	5	1	3	4	4	1

Table 3: Frequency of Adverse Events (AEs) per indication following initial implantation. *N*: number of patients per indication, (%): percentage of AEs for each indication. PD: Parkinson's disease, ET: essential tremor, OCD: obsessive compulsive Disorder STN: subthalamic nucleus ,VC/VS: ventral capsule/ventral striatum, Vim/PSA: thalamic ventral intermediate nucleus /posterior subthalamic area, ANT: anterior nucleus of the thalamus, GPi: globus pallidus internus, GPe: globus pallidus externus, VP: ventral pallidum, SSI: surgical site infection.

	N	Total no. of AEs (%)	SSI	Skin erosion	Wound dehiscence	Wire tethering	Peri-operative damage	Hematomas	Hardware migration	Hardware failure	Pain
PD	160	8 (5)	4	1	0	2	0	0	1	0	0
Epilepsy	8	1 (13)	0	0	0	0	0	0	1	0	0
ET	58	2 (3)	0	0	0	0	1	1	0	0	0
Dystonia	8	1 (13)	0	0	0	1	0	0	0	0	0
OCD	13	1 (8)	0	0	1	0	0	0	0	0	0
TS	58	4 (7)	1	0	0	0	0	2	0	0	1
Pain	0	0	0	0	0	0	0	0	0	0	0
Total	305	17	5	1	1	3	1	3	2	0	1

Table 4: Frequency of Adverse Events (AEs) per indication following IPG replacement. *N*: number of patients per indication, (%): percentage of AEs for each indication. PD: Parkinson's disease, ET: essential tremor, OCD: obsessive compulsive Disorder STN: subthalamic nucleus ,VC/VS: ventral capsule/ventral striatum,Vim/PSA: thalamic ventral intermediate nucleus /posterior subthalamic area, ANT: anterior nucleus of the thalamus, GPi: globus pallidus internus, GPe: globus pallidus externus,VP: ventral pallidum SSI: surgical site infection.

			Infection site			Bacteriologic profile							Infection site		
Treatment	Mean time-interval* *(days)*	Patients (N)	IPG#	Scalp	Mixed	Pos.	Neg	n.g.	n.a.	Treatment succesful	Secondary treatment (N)	Mean time-interval (days)**	IPG#	Scalp	Mixed
Antibiotics	58 (12-202)	14	6	5	3	8	0	4	2	42.9% (6/14)	Partial removal: 5 Complete removal: 3	64	5	0	3
Antibiotics + wound revision	102 (4-247)	7	4	3	0	4	1	2	0	85.7% (6/7)	Additional wound revision: 1	49	0	1	0
Antibiotics + partial replacement/ removal	165 (60-213)	4	3	1	0	2	1	0	1	75% (3/4)	Complete removal: 1	499	0	1	0
Antibiotics + complete removal		0								/	/				

Table 5: Management of hardware related infections. *Mean time-interval procedure (initial implantation/IPG replacement) to infection debute. ** Mean time-interval in days from initial treatment to secondary treatment (range). # IPG site: infraclavicular/abdominal. Pos. = gram-positive (S. aureus, S. capitis, S. epidermidis, Group B beta-hemolytic streptococci. Neg. = gram-negative (e. coli, Enterobacter cloacae, serratia marcescens). N.g. = no growth. N.a. = not available. n.g. = no growth.

	AE	p-value
Type of IPG		
Rechargeable	50% (2/4)	0.08
Non-rechargeable	17% (33/197)	
Micro-electrode recordings		
MER	17% (33/194)	0.43
No MER	29% (2/7)	
Procedure		
Staged	8% (3/40)	0.07
Non-staged	20% (32/161)	
Anesthesia		
General	19% (12/62)	0.73
Local	17% (23/137)	
IPG location		
Abdominal	19% (33/170)	0.80
Infraclavicular	7% (2/31)	
Target		
STN	20% (18/91)	0.74
VC/VS	15% (2/13)	
Vim/PSA	18% (6/33)	
Gpi/ANT	12% (7/57)	
GPe	0% (0/1)	
VP	33% (2/6)	
Duration of procedure		
Duration <4h	13% (6/46)	0.40
Duration >4h	16% (16/98)	
Location of electrodes		
Unilateral	13% (2/16)	0.59
Bilateral	18% (33/185)	
Fixation		
Burr hole cap	29% (8/28)	0.09
Cement	16% (27/173)	

Table 6: Surgical features and incidence of adverse events (AE). IPG: implantable pulse generator, MER: micro-electrode recordings, STN: subthalamic nucleus , VC/VS: ventral capsule/ventral striatum, Vim/PSA: thalamic ventral intermediate nucleus /posterior subthalamic area, ANT: anterior nucleus of the thalamus, GPi: globus pallidus internus, GPe: globus pallidus externus, VP: ventral pallidum SSI: surgical site infection.

Discussion

In this retrospective analysis we documented the hardware and surgery related adverse events relating of 201 consecutive DBS system implantations and 305 IPG replacements. Overall, there were 40 AEs (20%) following initial implantation of DBS hardware, of which 37 required additional surgery e.g. wound revision (11) and (partial) hardware removal and revision (18). Reports documenting AEs following DBS surgery remain equivocal with AE incidence rates ranging between 2.5 and 30.4%.[11,12,21–23] Consequently, an unambiguous reporting system was suggested based on three categories; intracranial AEs including hemorrhages and other intracranial AEs, SSIs, erosions and related AEs requiring partial or complete hardware removal and lead revisions for various reasons.[24] Further, Engel *et al.* proposed to report AEs, with the exclusion of intracranial AEs, in patient-years (mean follow-up * number of patients) rather than per electrode or implantation. As defined by the criteria in Engel *et al.* we observed, 2 (1%) intracranial AEs, 10 partial or complete hardware removals (1.5% per patient years) and 8 lead revisions (1.2% per patient years). When compared to the literature, the reported incidences are favorable: intracranial AEs (3.8%), partial or complete hardware removal (3.6%) and lead revisions (4.1%).[24]

The most common hardware related AE following initial implantation was SSI (10%), which is higher than the mean SSI incidence described in large systematic reviews of literature (4.7% - 5.12%) but within observed ranges (4.45 – 11.68; 0-15.2).[9,10,25] We found no association of selected variables i.e. obesity, smoking, diabetes. Our data does 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.[9] Specifically, we found no higher incidence of hardware related SSI requiring hardware removal for TS patients, which is in line with recent reports.[26] However, we recognize that a subset of these patients have a greater tendency to repetitively touch surgical wounds.[27] Further, in line with recent studies suggesting that externalization of DBS electrodes does not increase the risk of SSI, we found no difference in the incidence of SSI following staged or non-staged procedures.[28,29] In contrast with the literature, we were unable to associate surgeon's experience with the incidence of SSIs or AEs altogether.

Although patients were not treated according to a specified protocol, SSI treatment was aimed at preserving the DBS system. Initially, 64% of the patients that developed SSI received initial treatment with antibiotics only, which is considerably higher than reported in the literature (15%).[9] The patients who developed an SSI early after initial implantation were more likely to receive IV antibiotics alone, without the removal of the implanted devices. Here, we assume that this might be due to personal restraints of the treating clinician to withdraw the patients from their newly gained, long-wanted therapy shortly after implantation. Our results support previous reports that stimulation-sparing management of S. aureus may be ineffective as 6/8 cultures of patients requiring additional (partial) removal of the stimulation after IV antibiotics were positive for S. aureus.[30] S. aureus screening and subsequent decolonization may therefore be considered, as it has been shown to reduce DBS associated SSI incidence.[31] Initial treatment with IV antibiotics of SSIs involving multiple

sites failed. In these patients, surgical removal of infected hardware may be a better strategy. As antibiotic therapy was successful in four patients presenting with an isolated SSI of the scalp of which three over the lead entry wounds and one retro-auricular, we challenge the often adapted algorithm that an SSI over the brain electrodes always necessitates removal of all hardware.[30]

AEs following IPG replacement are rare, with incidence rates of hematoma, wound dehiscence, displacement and skin erosion varying around 1%.[32,33] Whether wire tethering complaints may be subscribed to an IPG replacement is debatable. However, the 3 patients with traction complaints after IPG replacement specifically localized the IPG site as the source of their pain. Incidence rates of SSI following IPG replacement vary in the literature; Sillay *et al.* reported an SSI rate of 0.5% in 208 IPG replacements, while Pepper et al. reported a higher rate of 10% SSI in 80 patients.[34,35] A larger multi-center cohort comprising of 1293 IPG replacement reported an SSI incidence of 2.3% per procedure, with possible under-reporting of minor superficial SSI.[33] We observed five SSIs following 305 IPG replacements (1.64%), which required IPG removal in two patients (0.67%). The low rate of SSI following IPG replacement is remarkable as recent study found 32% positive sonication cultures (23 of 71 patients in whom an IPG was replaced) for low virulent pathogens i.e. cutibacterium acnes.[36] We could not confirm previous findings that multiple IPG replacements increases the SSI rate as all IPG infections occurred in patients receiving brain electrodes before 2011 and previous IPG replacements in these patients could not be confirmed.

Strengths and Limitations

The principal limiting factor of this study is its retrospective design, where chart review may have resulted in lower AE rates, and lack of independent data monitoring. Prospectively and systematically recording AEs has been demonstrated to result in higher AE rates, with a recorded incidence rate up to 60.1%.[37] Few studies report systematically about AE's in clinical practice. Strengths of this study are its relatively large and unselected study population that includes the most common diseases treated by DBS.

Conclusion

The incidence of surgical and hardware related AEs following initial implantation of DBS hardware is within the range reported in current literature, with a higher mean rate of SSI in our center for which we found no clear explanation. We could not identify surgery or patient related factors that predisposed for developing surgical or hardware related AEs. Specifically, we found no differences following a staged or non-staged procedure or between DBS indications. The majority of patients with SSI were treated with isolated antibiotic therapy, which was unsuccessful in 57% of the cases. We have decided to apply a more aggressive treatment approach to SSIs involving multiple sites or when a S. aureus is identified. When

applying the three proposed categories for surgical and hardware related DBS AEs, our incidence rates of AEs are lower than reported in the literature. We support the need for a uniform reporting system for surgical and hardware related AEs in DBS surgery, which is useful for benchmarking. However, although clearly defined, the proposed categories may not be as useful for patient counseling as minor AEs will be under-reported.

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Chapter 8

Management of hardware related infections after DBS surgery: A cost analysis

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Abstract

Introduction

One of the most distressing hardware-related complications of deep brain stimulation is an 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.

Methods

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.

Results

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%.

Conclusion

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.

Introduction

As the number of implanting centers and the number of implanted patients grow in the field of deep brain stimulation (DBS), more and more data become available on its complications and their management. The complications can roughly be divided in surgery related, hardware-related and stimulation-related complications. One of the most distressing hardware-related complications is an infection. Usually these are low-grade infections at the implantation site of the internal pulse generator (IPG) and/or extension leads(3, 5, 21). Sometimes, the infection can move along the extension leads cranially towards the connectors or electrodes. The reported prevalence of hardware-related infections varies between 0.4 and 22.2% (7-9, 14, 22).

The management of hardware-related infections has been a topic of investigation in our center for some time(18). For infections located at the site of the IPG and/or cables, which is the vast majority of the infection cases, we treated either with antibiotics for several weeks or performed immediate removal of the infected hardware followed by reimplantation. In our experience the success of antibiotic therapy was about 50%(18), while the surgical approach provided a more definitive solution as expected.

The choice for one or other strategy depends on preferences of the DBS team and individual patient. However, another factor that influences decision-making is the cost of the two approaches. In this study, we investigated the costs of treatin g the infection with antibiotics only with the risk of surgery when unsuccessful versus immediate removal followed by reimplantation.

Methods

Study design

Cases of DBS hardware related infections were identified in the time period between 2004-2014. All cases were treated at the Maastricht University Medical Center (MUMC). For the analysis of costs, only relevant hospital costs that were incurred in the course of treatment were considered. Other healthcare costs, patient and family costs or costs in other sectors were not included.

Patient selection

Medical records of patients were reviewed in detail and demographic data were collected including age, sex and diagnosis. Data on the post-operative infections including the type, localization, microbiology and treatment were recorded. Details of the surgical approach have been described earlier (12, 19).

Any infection that occurred after a DBS-related surgical procedure, like implantation or IPG replacement was included into the analysis. Infections were confirmed via clinical suspicion (i.e. redness, swelling, or warmth with either elevated body temperature and/or inflammatory markers) and/or proven microbiological cultures of purulent exudates collected from the suspected site of infection.

Cost identification

Costs were identified by expert opinion for each treatment option. The following costs were included into the analysis: cost of an inpatient day in an academic hospital (which includes cost of a medical specialist, an assistant doctor, nursing staff, materials and nutrition, medication, housing, equipment and overhead costs, costs for antibiotic treatment, costs for an IPG replacement (including operating theatre costs), costs for determining the microbiological cause of an infection (culture and antibiograms) and costs for checking infection parameters (e.g. C-reactive protein and leukocyte count) (Hakkaart-van Roijen et al., 2015).(11)

Cost volumes

For all the identified costs, volumes were determined for each treatment option. For cases of DBS hardware infections that are treated successfully with intravenous antibiotics only, the following volumes of costs were included: fourteen inpatient days, one determination of the cause of infection and three times checking of infection parameters (once at the initiation of treatment and once a week during the course of treatment). For cases of DBS that were treated by immediate surgical replacement, cost volumes were including five inpatient days, one determination of the cause of infection, once checking of infection parameters and one IPG/cable(s) replacement surgery.

Cost valuation

All costs were indexed as 2015 Euros. The 2014 reference price for an inpatient day was used (Hakkaart-van Roijen et al., 2015).(11) Other costs were valued by using 2012 MUMC cost prices when available and otherwise by 2012 tariffs set by the Dutch Health Authority. (1) Costs of antibiotics were valued using the cost price for Flucloxacillin.(2) Cost prices were indexed to 2015 by means of consumer price indices of the Dutch Central Bureau of Statistics. An overview of costs and cost prices is given in Table 1.

Cost	Price (€)	Source
Inpatient day in academic hospital	646	Reference price (Hakkaart-van Roijen et al., 2015)
Checking infection parameters	16	Combination of Dutch Health Authority tariffs and MUMC cost prices
Determining the micro-biological cause of infection	43	Combination of Dutch Health Authority tariffs and MUMC cost prices
IPG replacement (incl. operating theatre costs)	26012	MUMC cost price
Flucloxacillin (price per day)	27	Reference price (medicijnkosten.nl)

Table 1. An overview of costs and cost prices. Cost prices were indexed to 2015 by means of consumer price indices of the Dutch Central Bureau of Statistics

Sensitivity analysis

A sensitivity analysis was performed to assess the influence of varying the success rate of treatment with antibiotics alone.The average cost per patient was calculated for percentages of cases of DBS hardware infections successfully treated with antibiotics alone varying between 0 and 100%. Furthermore, since the reference price for an inpatient day includes the medication costs;a sensitivity analysis was performed that excluded the additional costs for intravenous antibiotics.

Patient	Sex	Age	Disease	Surgery	Infection (days after surgery)	Pathogen	Location of infection	Treatment	Antibiotics
1	M	64	Tremor	Bilat T	7	Unknown	PG	Antibiotics/Surgery	Clindamycine
2	F	51	PD	Bilat STN	135	S.Aureus	PG	Antibiotics/Surgery	Floxapen/Rifampicine
3	F	43	Tremor	Bilat T	57	S.Aureus	PG	Antibiotics/Surgery	Clindamycine
4	M	44	PD	Bilat STN	184	Unknown	PG + Extension cables	Antibiotics/Surgery	Floxapen/Rifampicine
					Unknown	Unknown	PG	Surgery	
5	M	60	PD	Bilat STN	224	Unknown	PG + Extension cables	Antibiotics	Floxapen/Rifampicine
					481	Unknown	PG + Extension cables	Antibiotics/Surgery	Floxapen/Rifampicine
6	F	63	PD	Bilat STN	22	Unknown	PG	Surgery	
7	M	41	Tourette	Bilat T	35	S.Aureus	PG	Antibiotics	Floxapen/Rifampicine
8	M	35	Tourette	Bilat T	14	S. Aureus	Extension cables	Antibiotics	Cefazolin/Rifampicine
9	F	60	PD	Bilat STN	760	S.Aureus	PG	Antibiotics	Floxapen/Rifampicine
10	M	64	PD	Bilat STN	490	Unknown	PG	Surgery	
11	M	68	Tremor	Bilat STN	378	Unknown	PG	Surgery	

M: male, F: female, PD: Parkinson's disease, STN: nucleus subthalamicus, bilat: bilateral, T: thalamus, PG: pulsgenerator

Table 2. Patient characteristics. F: female; M: male; PD: Parkinson's disease; Bilat T: bilateral thalamic DBS, Bilat STN: bilateral subthalamic nucleus DBS; PG: internal pulse generator

Results

Cases of DBS hardware infections

Between 2000 and 2012, 156 patients (306 electrodes) underwent DBS surgery for movement disorders, epilepsy and psychiatric disorders. The number of surgeries in this cohort was 376 (158 primary DBS surgeries and 218 IPG replacement surgeries). We identified thirteen infections in eleven patients who developed an infection of the implanted DBS hardware. These patients were diagnosed as Parkinson's disease (PD) (n=6), tremor (n=3) or Tourette syndrome (n=2). Overall, the infection risk was 3.5%.

Four out of thirteen infections included in the analysis were successfully treated with intravenous antibiotic treatment. In five cases, antibiotic therapy was unsuccessful. They required surgical removal of the infected DBS hardware and subsequent replacement. Remaining four cases of infection underwent immediate removal due to the surgeon's preference without antibiotic therapy attempt (Table 2).

These results show three different outcome options in our series. In the first scenario, patients were successfully treated with intravenous antibiotic therapy and did not require removal and reimplantation of hardware. The second scenario was an unsuccessful antibiotic therapy and led to removal of hardware and later reimplantation of hardware. The last scenario was immediate removal of infected hardware, antibiotic treatment followed by reimplantation of new hardware.

Costs

Figure 1 shows the different treatment options and corresponding total costs per case. The costs of treating a case of DBS hardware infection with an immediate IPG replacement surgery are €29,301. The costs of a successful treatment with antibiotics only are €9499. When treatment with antibiotics fails to resolve the infection and surgery to replace the IPG is required, the total costs of the treatment are then €38,741.

Although antibiotic treatment was initiated in nine cases of DBS infections, it was only successful in resolving the infection in four cases. The remaining five cases had to undergo surgery. This results in average treatment costs per patient of €25,745. In other words, trying to resolve DBS hardware infections initially with antibiotics reduced treatment costs by 12.1%.

Sensitivity analysis

Average costs per patient, following our decision model, decrease linearly when the success rate of treatment with antibiotics alone increases. In a scenario where 10 patients present themselves with a DBS infection that are all treated with antibiotics alone, each patient who can be successfully treated with antibiotics (thereby preventing subsequent surgery) will reduce average treatment costs per patient by €2924.

Discussion

Here, we investigated the costs of treating hardware-related infections of DBS with antibiotics with a good chance of success versus direct removal followed by reimplantation of hardware. This study therefore explores the possibility of cost-reduction by treatment of hardware related infections with antibiotics. Our results show that the antibiotic therapy approach in our series resulted in a reduction of circa 12.1%. These findings support the strategy of managing these infections with antibiotic treatment.

Successful treatment of a DBS hardware infection with antibiotics only was found to be substantially less costly than IPG and extension replacement surgery (18). Nevertheless, we should interpret our findings with caution. For these savings to be realized, about half of the patients for whom the treatment with antibiotics was initialized had to be successful. These results might vary from center to center and need confirmation in larger cohorts. In addition, two weeks of hospitalization may have caused distress which has not been valued in the current study. As our model demonstrated that savings in treatment costs increase linearly with the success rate of antibiotic treatment, it did not include patient specific comorbidities which may influence the success rate of antibiotic treatment. Future research, including more rigorous sensitivity analyses, should emphasize on identifying patient specific factors that may determine the success of antibiotic treatment. When it is known beforehand in which cases antibiotics treatment is most likely to be successful, then a tailored treatment modality can be offered to patients resulting in greater cost savings.

There is a high variation in the infection rates reported in the literature. The question arises which factors influences the infection rate. Recent findings indicate that the infection rate is not influenced by patient age, sex or the approach used for the initial surgery (a two-stage procedure vs. implantation simultaneously with leads or surgery in conventional suite vs. MR-equipped suite) (3, 6, 13, 16, 17). However, in another study a younger age was identified as a risk factor for the development of an infection (10). The pre-existence of scalp erosion, longer duration of surgery, and the higher number of people in operating room during surgery are found to be risk factors for a delayed infection (20). Compulsive manipulation of the wounds as observed in patients with Tourette syndrome or obsessive-compulsive disorder is a well-known risk factor for wound complications and hardware infections (15). Other potential risk factors for hardware related infections are systemic comorbidities

causing immune-suppression (diabetes, autoimmune diseases, etc.) (7). Staphylococcus aureus infections of the IPG can be more resistant to antibiotic therapy. In this case, some authors tend to remove hardware immediately (4), which has not been our policy.

Conclusion

Here, we investigated the costs of treating hardware-related infections of DBS with antibiotics versus direct removal followed by reimplantation of hardware. Our results show that initial treatment with antibiotics without immediate hardware explantation results in reduced costs. The implementation of a therapeutic algorithm for the management of hardware related infections after DBS is essential for limiting the impact and severity of these complications.

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Chapter 9

Discussion

Deep brain stimulation for OCD: an established therapy?

OCD causes considerable disability. The Global Burden of Disease studies assessed the burden of all anxiety disorders, rather than including specific disorders such as OCD, from 2010 and onwards, considering the high degree of comorbidity across anxiety disorders. In 1990 The World Health Organization estimated OCD to be the 11th leading cause of nonfatal disease burden in the world, accounting for 2.2% of total Years Lost to Disability (YLD= the number of years with a lower quality of life due to the disease).[1] In the 2017 WHO report 'Depression and other common mental disorders', anxiety disorders, among which OCD, are listed as the sixth largest contributor to non-fatal health loss globally, with a global 24.6 million YLD. If patients with OCD fail to respond to CBT, two SSRI trials, clomipramine and additional therapy with antipsychotics, they can be considered treatment refractory. It is estimated that approximately 40 to 60% of the patients remain treatment-refractory, commonly defined as a less than 25% reduction on the Y-BOCS after treatment, which urges the need for alternative treatment strategies, such as electrical stimulation of subcortical structures e.g. by way of deep brain stimulation (DBS) *or* ablative interventions such as Gamma Knife Ventral Capsulotomy (GVC).[2]

In 2014, the Neurosurgery Committee for Psychiatric Disorders of the World Society for Stereotactic and Functional Neurosurgery (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." In 2021, the taskforce recognized two such blinded randomized controlled trials, both using DBS of the ventral anterior capsule region, with only one study considered to be of level I evidence According to the Canadian Task Force on the Periodic Health Examination's Levels of Evidence.[3–5] As a consequence, the WSSFN stated that electrical stimulation for otherwise treatment refractory OCD using DBS in the ventral anterior capsule region (including bed nucleus of stria terminalis and nucleus accumbens) remains investigational, rather than an established therapy. Although the classification of the study of Denys et al. as level II evidence is a matter of debate and the publication of third RCT aimed at stimulating the same brain region since, we recognize two supplementary requirements (causality and cost-effectiveness), in addition to an acceptable risk-benefit ratio, before DBS can be concluded an established rather than emerging treatment for otherwise treatment refractory OCD.[6,7] Of note, the Dutch Healthcare Authority (NZa) established DBS for patients with refractory OCD eligible for reimbursement in 2013.[10]

Thus, we identify four pillars upon which an established therapy of severe therapy of refractory OCD should rest: 1) Efficacy and functional outcome 2) Safety 3) Causality and 4) Cost-effectiveness. In this general discussion, we will discuss current evidence, how this thesis contributed to the strengthening of these pillars and in what way it was limited in doing so, and future challenges and opportunities. Of note, considering the pith of matter of this thesis and the absence of high quality evidence in GVC we will limit this part to DBS. We refer to the impact section of this thesis in which we elaborate on the fourth pillar: cost-effectiveness of DBS for OCD.

Efficacy and functional outcome

To date, eight studies that included randomized, controlled assessments of DBS in a total of 78 OCD patients have been published.[3,4,6,8–12] However, most of the literature on effectiveness of DBS comprising around 200 patients, consists of uncontrolled case reports, series or trials, as reviewed elsewhere.[13–15] In addition to the two studies identified by the WSSFN, the American Society For Stereotactic and Functional Neurosurgery Association of Neurological Surgeons (ASSFN)/Congress of Neurological Surgeons (CNS) recognizes Mallet et al. (2008) aimed at stimulating the subthalamic nucleus, to meet the criteria of level I and II evidence according to the Canadian Task Force on the Periodic Health Examination's Levels of Evidence.[5] As will be discussed below, these three adequately reported placebo-controlled randomized controlled trial studies mark the efficacy of OCD-DBS based on a mean Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) reduction and corresponding response rate, but only modest effects of DBS have been observed on global functional or disability scores.[3,12,16] Especially in severe OCD patients a more holistic approach towards evaluating treatment outcome is warranted and therefore should include a measure of global functioning. Frequently used functional or disability scores are the Global Assessment of Functioning (GAF) (range 0-100) and the Sheehan Disability Scale (SDS) (range 0-30). Both scales were developed to asses functional impairment in the social, occupational and personal domains.[17,18] The GAF clusters these domains in 10 anchor points with scores on the lower end indicating that the individual is having severe difficulty with daily activities and functions and may be a danger to themselves or others, and higher scores representing an individual with minimal difficulty in daily functions. Whereas the SDS scores each domain on a 0-10 scale, with higher scores indicating greater functional impairment.

In Luyten et al. (2016), 17 patients completed the double-blind crossover trial with two arms lasting 3 months each.[4] At the end this trial the median improvement in YBOCS was 45%. Median GAF scores improved from an estimated score of 35 at baseline to a score of 65 at last follow-up. A score of 60 on the GAF translates in the persistence of, albeit mild, symptoms or difficulty in social, occupational or school functioning.

Mallet et al. (2008) enrolled 16 patients in a double -blind, cross-over design with two 3-month phases.[12] Following active STN DBS, YBOCS scores were significantly lower than sham stimulation, independently of the group and the period (mean ±SD, 19±8 vs.28±7; p=0.01). GAF scores were also found to be significantly higher (56±14 vs. 43±8, P=0.005). Nevertheless, no differences were found in SDS scores. A GAF score of 56 however, implicates the presence of moderate symptoms or problems in social, occupational or school functioning.

In the double-blind cross-over controlled study of Denys et al (2010), 16 patients were randomized to receive either active or sham stimulation of a period of 2-weeks, followed by a second cross-over period preceded by an open 8-months treatment phase. The study ended with an open 12-month maintenance phase.[19] At the end of the maintenance phase a mean improvement of 17.5±8.3 of total Y-BOCS scores were observed. Patients also reported improvement in three domains of the SDS compared to baseline: work 8.9±1.1 vs. 4.1±3.2, social life 9.0±1.0 vs. 4.7±2.6 and family life 4.0±2.7. A score of 4-6 on the SDS resembles a moderate disruption of the associated domain. In our retrospective cohort as presented in **chapter 2**, 8 patients received a median stimulation of 26 months and exhibited a mean Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) reduction of 10.5. Defined as a ≥35% Y-BOCS reduction at the time of last-follow up, five patients were considered to be a responder while 3 remained non-responding resulting in a response rate of 63%. Although the patients in this study reported an increase in self-reported health, no general functional outcome measures were included.

These clinical studies collectively report DBS as an effective and safe treatment option for treatment- resistant OCD patients. Obviously, our retrospective case report does not correspond to the level of evidence as observed for the studies by Denys et al. (2010), Luyten et al. (2016) and Mallet et al. (2008) lacking randomization and non-blinded assessment including a low number of patients. However, this sample sizes in the RCTs as presented were only a double of the amount of patients included in our case study. Moreover, the ON-OFF paradigm remains not undisputed as period effects and carryover effects are frequent yet not systematically assessed confounding factors characteristic of this study design. Period effects occur when the effect of stimulation differs between the ON–OFF group and the OFF–ON group.[20] Carryover effects refer to the possibility that the effect of the intervention provided in the first period extends into the second intervention period, a risk that is ideally minimized by an appropriately long washout between the different intervention arms. Furthermore, it is well-documented that some of the effects and side effects of DBS occur very rapidly, thus possibly giving rise to problems with blinding, especially during the second period of the study.[21] Despite these issues, crossover designs in the context of DBS surgery are valuable ways of accounting for potential placebo effects, as they control for information bias and address the aforementioned ethical concerns of insertion or non-insertion of the device itself.[22]

Despite these limitations, together with an improvement of OCD symptomatology expressed as YBOCS scores reductions, improvements in global functioning are observed. However, mild-to-moderate impairment in global functioning persists after treatment. Several causative factors attributing to this impairment may be identified.

First, this persistence of impaired global functioning may be confounded by the persistence of treatment refractoriness i.e. is caused by the non-responding patients or the presence of (severe) concomitant Axis I disturbances such as depression or anxiety. Although Luyten et al. identified GAF scores to be dependent on stimulation condition, none of the studies explicitly associate functional outcome with OCD severity or Axis 1 co-morbidity. Second, as fueled by the absence of SDS improvement in Mallet et al., the sudden event of patients being "cured" (i.e. the remission or drastic improvement of symptoms) following DBS in situations of decades of multiple drug attempts and CBT may impose the 'burden of normality'. The 'burden of normality', is defined as difficulty in adjusting to being free of significant symptomatology.[23] In other words, the 'burden of normality' can arise when a transition in self-concept occurs, associated with the shift from chronic disability to sudden wellness. Although rarely discussed in the light of OCD, this concept is helpful for highlighting the management of expectations of normal living and the transitioning self-concept post-DBS.[23] Third, inclusion criteria for DBS, as proposed by Nuttin et al., only select the most severe cases of OCD with Y-BOCS scores of at least 30 persisting for a minimum of 5 years.[24] For such profound OCD symptoms, complete functional recovery may simply not be feasible. Considering a substantial functional impairment in and treatment resistance of mild to moderate OCD (Y-BOCS scores of 20-30) one may speculate that the true therapeutic potential of DBS for OCD remains yet to be identified.[25,26]

Taken together, to answer the question whether DBS is an efficacious therapy for refractory OCD one must first clarify what the desired effect is. From a clinician's perspective this would include a reduction of OCD symptomatology as expressed by the score on the Y-BOCS. Five main aspects: frequency or time spent, degree of interference, distress, resistance and perceived control, of both obsessions and compulsions are scored on a 0 (no symptoms) to 4 (extreme symptoms) scale summed to yield a maximum of 40 points.[27] Severe to extremely severe OCD is thresholded at a Y-BOCS score of 35-40, moderate to severe symptoms correspond with scores of 26–34, moderate symptoms rate at scores of 14–25 and scores of 0-13 correspond with mild or subclinical symptoms of OCD.[28] Although the Y-BOCS is widely used and studies report good internal consistency and test-retest reliability, it is not undisputed.[29] First, the organization of the Y-BOCS assessment implies a second order structure, the total severity score (sum of all items), is the result of the sum of severity scores related to obsession (sum of the first five items) and compulsion symptoms (sum of the last five items). Although patients reporting isolated obsessions or compulsions are rare, obsession (30%) or compulsion (20%) dominant OCD phenotypes exist.[30] In these conditions, the total Y-BOCS score may an underestimation of disease severity e.g. an OCD

patient with obsessive dominance may be extremely affected by the obsessions in terms of time spent, degree of interference, distress, resistance and perceived control, but (in absence of compulsions) the total Y-BOCS score result would be 20 out of 40, interpreted as 'moderate' OCD.

The second main concern regarding the Y-BOCS' psychometric properties is item factor loading. Factor loading is defined by the relationship between items and latent variables, allowing the identification of items that may not be relevant because they do not fully represent the factor being measured.[31] Specifically for item 4 (resistance) of the Y-BOCS: individuals with OCD who always make an effort to resist, as well as those who do not need to resist their obsessions, receive a lower score. As a result these patients are qualified to have less severe symptoms than those who willingly yield to the unwanted thoughts. In this sense, these items do not add information about the phenomena the scale is trying to measure (symptom severity). Therefore, these items may be adding noise to the Y-BOCS severity score. A recent factor analyses presented the lowest correlation coefficients of both resistance (obsession and compulsion) scores among all items with the OCD severity scores.[31] These results suggest that resistance items may not explain OCD severity adequately. In line with this, when using the Y-BOCS for treatment evaluation, clinical experience learns that these scales do not yet capture all the relevant changes that patients experience during DBS treatment. Illustratively, if time spend on compulsions improves from 16 to 9 hours, it will give the same score. Moreover, the general level of anxiety and stress is insufficiently taken into account, as is the *experience* of the time spend on compulsions. That is, it makes a great difference if one feels continuously anxious and stressed during the performance of the compulsive behavior, or whether one still performs the behavior but without this tension and pressure.[32] Further, the Y-BOCS does not include an aspect of avoidance. That is, if patients would avoid events that would provoke compulsions afterwards, they would score lower on the Y-BOCS.[32] Traditionally, both a person's avoidance behavior and his or her subjective units of distress have been captured by the Behavioral Avoidance Test (BATs).[33] Although the BATs exhibit good treatment sensitivity, they are difficult to design given the wide range of feared situations within and across individuals with OCD. Together these and the aforementioned caveats of the Y-BOCS and global functional outcome measures foster the idea of introducing alternative measures of treatment outcome such as patient-reported outcome measures (PROMs) using Ecological momentary assessment (EMA) methods. PROMs are unique indicators of the impact of disease on patients, and can empower patients by giving them a voice and decision-making capacity in evaluating the efficacy of treatment, its side effects, and affordability.[34] Examples of generic PROMS instruments include the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)10 and the World Health Organization Quality of Life BREF (WHOQOL-BREF).[35,36] Condition-specific instruments such as the Obsessive-Compulsive Inventory (OCI) mainly evaluate symptom domains directly associated with OCD.[37] These instruments (including the Y-BOCS) rely on a patient's ability to retrospectively recall

behavioral dimensions of problems, they presuppose that a patient's recall is reasonably accurate, although this may be incorrect. Ecological momentary assessment (EMA) is a method for collecting data in real-time and in real-word in order to avoid this retrospective biases and collects ecologically valid data, and enables study behavioral processes over time.[38] Recently, EMA based PROM questionnaires have been suggested to demonstrate treatment effects of OCD therapy.[39] However, future studies are warranted to establish the reliability, validity and feasibility of such questionnaires.

Safety

Safety can be expressed as the absence of Adverse Events (AEs) AEs may be device-related, i.e. caused by the device or the procedure, or related to stimulation parameters. Although the aforementioned randomized controlled trials collectively only report one serious AE related to a parenchymal brain hemorrhage and no remarkable cognitive changes during neuropsychological assessment were observed, they are generally limited by the number of patients.[3,4,12] It may therefore be of interest to consider larger, prospective cohort studies when assessing the safety of DBS for resistant obsessive-compulsive disorder.

Denys et al. (2020) enrolled seventy consecutive patients, including 16 patients from the trial mentioned above, to receive bilateral DBS of the ventral anterior limb of the internal capsule (vALIC).[3,40] Two patients required complete hardware removal and subsequent re-implantation due to hardware infection (3%), with another two patients treated with oral antibiotics as a result of superficial infection of one of the cranial incisions. Other hardware related AEs requiring revision surgery included malpositioning (6%), migration (1%). Minor hardware related AEs included headache (36%), wire-tethering (30%), and paresthesia (20 and pain around the burr holes (17%). The main stimulation-related adverse events were transient hypomanic symptoms (39%), including restlessness (33%), agitation (30% of which 3% permanent), impulsivity (19%), and sleeping disorders (46% of which 7% permanent). Most of these symptoms were noted to be related to changes in stimulation and lasted between several days and several weeks. On suicide attempt was classified as a stimulation-related adverse event because the attempt occurred 1 day after a DBS voltage increase of 0.5V.

In the prospective multi-center study by Menchón et al (2019), the safety and efficacy of Anterior limb of the Internal Capsule (ALIC) DBS was examined in 30 patients.[41] An AE was defined as any untoward medical occurrence, unintended disease or injury or untoward clinical signs in patients, whether or not related to the DBS system. AEs did not include reprogramming of the DBS system due to lack of efficacy, transient undesirable stimulation-produced effects, any normal expected postoperative complaints or symptoms (up to 30 days post-operative) if they did not require interventions differing from ordinary

postoperative care. A serious AE was defined as any AE that led to death or serious deterioration in the health of the patient that either resulted in: a) a life-threatening illness or injury, or b) a permanent impairment of a body structure or a body function, or c) in-patient or prolongation of hospitalization, or d) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function. Consequently, all patients experienced AEs, with a total 195 AEs with the majority considered to being mild ($n = 102$, corresponding to 52% of AEs) or moderate (73, 37%). A total of 36 SAEs was reported by 16 patients (52%), including OCD worsening (29%), followed by seizures (13%) and anxiety and hypomania (6%).

Both studies conclude DBS of the ALIC as an effective and safe treatment for patients with therapy-refractory OCD. However, it is suggested that emerging indications such as OCD may be more prone to undergo DBS hardware related complications when compared to e.g. Parkinson's disease.[42] In **chapter 7** we provide a direct comparison of surgical and hardware related AEs between indications in 201 implantations including 13 OCD-patients. We were not able to identify OCD patients being more susceptible for surgical or hardware related AEs when compared to DBS for movement disorders. Although Menchón et al (2019) define, code and cluster AEs according to contemporary standards, consequent observed AEs impose serious meta-analytical challenges and may be implausible from a clinical perspective as illustrated by the observation of the occurrence of AEs in all included patients and exemplified by OCD worsening being categorized as a SAE. **In chapter 7**, we acknowledge the need for an unambiguous reporting system of surgical and hardware related complications of DBS. Both Denys et al. and Menchón et al. did not include cognitive safety as an outcome measure. In **chapter 5** we provided a systematic review and case-series which assessed the cognitive safety DBS for OCD. In the systematic review, five randomized controlled trials and nine observational studies comprising a total 171 patients were analyzed collectively. These studies, generally did not report cognitive deterioration after DBS for OCD. Unfortunately, the variability of study designs and the multitude of cognitive measures precluded a meta-analysis to confirm its safety *or unsafety*. Considering the ambiguity in reporting the surgical and hardware related-, stimulation related or neuropsychological assessment, we propose the use of PROMs as an additional measure for DBS therapy safety. This will allow e.g. to weigh cognitive or stimulation related side effects with patient reported outcome and guide clinical decision making. Ultimately the use of feedback of patient reported symptoms and side effects could result in reduced symptom severity and improved health related quality of life as is observed in patients receiving treatment for advanced cancers.[41]

Causality

Causality is the relationship of cause and effect. Here we use it as an umbrella term to describe the therapeutic effect of DBS that may be attributed to electrical stimulation, a possible cognitive pattern through which the efficacy of DBS for OCD might be explained, and the anatomical specificity of DBS treatment.

In all treatments in medicine, there is the need to discriminate between the therapeutic benefit due to the intervention "per se" and that due to other inherently related factors such as the placebo effect. The placebo effect refers to the portion of therapeutic effect mainly mediated by the expectation of benefit that is inherently triggered in the patient. As for DBS, the surgical procedure per se is not intended to cause any benefit, but it is merely the vehicle for the therapeutic effect of electrical current. Nevertheless, in PD patients who are awake during the implantation surgery, immediate motor symptom alleviation may be observed, referred to as the microlesion effect (MLE). In the attempt to control for placebo responses, several studies adopted randomized, blinded crossover designs, in which patients are randomly assigned to either real (ON) or sham (OFF) stimulation, and then switched to the other condition in the second part of the study. The aforementioned studies of Luyten et al. (2016), Mallet et al. (2008) and Denys et al (2010) included a blinded crossover design of 3 months and 2 weeks respectively through which the placebo or microlesion effect could be assessed.[3,4,12]

In the study of Luyten et al. (2016) patients showed a significant improvement (median: 37%) in Y-BOCS scores when comparing the blinded ON phase (median Y-BOCS score: 20) with the blinded OFF phase (median Y-BOCS score: 32). Thirteen out of 17 patients also had improved Y-BOCS scores (median improvement: 11%) during the OFF phase as compared with the preoperative situation (median Y-BOCS score: 35).[4] In Mallet et al Y-BOCS scores was significantly lower at the end of the active stimulation than at the end of the sham stimulation (mean score, 19±8 vs. 28±7; P = 0.01), independently of the group (ON-OFF vs. OFF-ON) or period. Lastly, Denys et al. (2010) observed an additional effect of active stimulation of 8.3 (±2.3) points on the Y-BOCS scores or 25%. The studies collectively conclude that the beneficial effect is indeed caused by electrical stimulation and is not a mere (placebo) effect of implantation. Considering the observed beneficial effects of OFF-stimulation compared to baseline they do not rule out the existence of a micro lesion/ placebo effect. However, none of them explicitly focused on the magnitude of non-stimulation-related therapeutic effects. Our group recently addressed this in an individual patient data meta-analysis. Here, we found that sham-stimulation induced a significant change in Y-BOCS scores of about 5 points, which constitutes a meaningful clinical difference.[43]

To date, several explanatory cognitive frameworks for OCD are postulated. These include deficiencies of goal directed behavior, habit formation and impaired cognitive flexibility.[44] In

Chapter 5, through a systematic review and case-based analyses, we aimed to increase our understanding of the cognitive working mechanism of DBS by identifying a cognitive pattern associated with symptom reduction. As mentioned above, the data was too inconsistent to recognize a cognitive pattern that is associated with better outcome, or would (in part) explain the efficacy of deep brain stimulation for OCD. However, multiple studies observe an improvement of cognitive flexibility regardless of the stimulation target. Cognitive flexibility has been defined as the ability to flexibly adjust behavior to the demands of a changing environment. Different aspects of cognitive inflexibility have been probed using a wide variety of neuropsychological test including tests for attentional set shifting, task switching, reversal learning, and response inhibition.[46]

Attentional set shifting comprises the ability to switch attention from one aspect of a stimulus to another in an ongoing task in accordance with changing reinforcement contingencies.[46] This is commonly probed using the Intradimensional/Extradimensional Shift Task (IED) from the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the Wisconsin Card Sort Task (WCST). OCD patients show consistent deficits in both tasks.[44] Attentional set shifting deficits are correlated with hypofunction of the right dorsolateral prefrontal cortec (dlPFC) as measured with FDG-PET.[47] More recently, Vaghi et al, reported reduction of functional connectivity between the caudate and the (ventrolateral) prefrontal cortex that was selectively associated with reduced attentional set-shifting.[48] OCD patients selectively failed at the extra-dimensional stage of the IED. This means that they are able to apply a rule within the same dimension but have problems applying that same rule to another, previously irrelevant dimension.

Task switching describes situations in which subjects must change strategy based on an explicit instruction or cue, rather than inferring changed contingencies from the pattern of reward receipts.[46] Typically, task switching, which requires shifting attention, is probed with the Trail Making Test part A or B (TMT-A/B). This is another tasks in which OCD patients consistently show deficits.[44] During task switching OCD patients show a reduced activation of the dlPFC and the orbitofrontal cortex (OFC) compared to healthy control subjects.[49,50]

Reversal learning, a variant of RL, examines the ability to adapt the response to a change in learning contingencies. Using a reversal learning paradigm Chamberlain et al. showed a decreased activation of the lateral OFC, lateral prefrontal cortex (PFC) and parietal cortex in OCD patients and their unaffected relatives, compared to healthy control subjects.[51]

Finally, OCD patients show deficits of response inhibition on the Stroop Color Word Test (Stroop CWT) and the stop signal reaction time task (SSRT) - but not in the go/no go task. Whereas the latter two probe prepotent motor response, the Stroop CWT measures the inhibition of an innate prepotent cognitive response (i.e. reading of text). The subthalamic nucleus (STN) has been extensively related to the SSRT, as projections from the PFC to the STN inhibit the thalamic output to the primary motor cortex (the so called 'hyperdirect

pathway').[52] The relationship between choice strategy in terms of RL and response inhibition was recently investigated by Jahfari et al.[53] Connectivity analysis showed that longer SSRTs were associated with a reduced connectivity between the PFC and the subthalamic nucleus (STN), especially in participants which showed the most uncertainty, and therefore utilized the most exploitative learning strategies. In conclusion, as emphasized throughout the discussion in **chapter 5**, much remains unclear, especially considering the questions whether cognitive inflexibility resembles a distinct pathology in OCD patients or in what way cognitive flexibility contributes to a relieve in symptomatology.

Using the novel approach of *fiber filtering* or *discriminative tractography* applied to a normative connectome we were able to identify streamlines connecting the lateral and medial prefrontal cortex with the anteromedial STN and medial dorsal (MD) nucleus of the thalamus were predictive of successful VC/VS DBS **(Chapter 2)**. As reviewed in **chapter 3**, these results were validated and refined in multiple cohorts with different DBS target regions (ALIC/NAc, BNST and STN), thereby identifying a novel network model including hyperdirect connections of medial and lateral prefrontal cortices to the STN and projections between the anterior thalamus and PFC both converging in the central ALIC for an underlying mechanism of neuromodulation for OCD. However, precise organization and termination points of this pathway remain unclear. As outlined in **chapter 3**, the dACC can be considered a strong candidate. Crucially, modulation of this circuit could take place at different nodes of the network: via DBS to the ALIC, STN, thalamus, and, potentially, the GPi. Based on the fact that different targets are equally capable of modulating this specific network, one may argue that these different targets within this loop are therefore interchangeable. However, as illustrated in a recent clinical trial including both the ALIC/NAc and the STN target in the same patients, different structural connectivity of these targets exist, and are associated with modulation of different networks and functions.[56] Indeed, while ALIC/NAc DBS had a greater effect on comorbid depression and STN-DBS was associated with improved cognitive flexibility. Finally, although evidence from available studies remains scarce, the concept of a common network for improving OCD symptoms may be independent of the disorder. Comorbid obsessions and compulsions in patients suffering from Tourette Syndrome improve when the central ALIC pathway is stimulated.[57] Thus, the proposed network may be effective in improving obsessions and compulsions, rather than OCD (as a categorical disease). Importantly, OCD is a highly heterogeneous disorder. Apart from specific OCD subtypes, e.g., washing, checking, etc., the putative underlying neuropsychological mechanisms are also widespread, e.g., impaired habit vs. goal-directed behavior, cognitive inflexibility, emotional vulnerability or altered risk evaluation. These underpinning principles may in turn serve as transdiagnostic dimensions for other compulsivity-related disorders, such as behavioral addiction, substance use disorders, Tourette Syndrome and autism-related stereotypes. Thus, a next step for a more effective and personalized neuromodulation for OCD will be to characterize these endophenotypes and identify through which networks each may be effectively modulated.

The identification of a common network for improving OCD symptoms offered the opportunity to re-evaluate clinical non-responders in our cohort. Although being restricted by the absence of pre-operative, patient specific, diffusion weighted MR-images, we selected 3 patients with at least 1 year of stimulation, who showed inadequate or no-response to VC/VS stimulation at last follow-up, despite extensive programming sessions. Optimal stimulation parameters and DBS electrode contacts were then determined in MNI-space by calculating the greatest volume of overlap between the optimal ALIC streamlines and the simulated Volume of Tissue Activation. This method reduced the amperage or voltage with at least 50%, thereby potentially increasing DBS-battery longevity. Although preliminary, 1 patient showed an improved clinical response after 3 months.

Future challenges

After initiating DBS many patients still require medication and/or behavioral therapy to deal with persisting symptoms and habitual behaviors. In **chapter 8** we discuss the effectiveness, timing and procedural aspects of CBT added to DBS through a systematic review. In this chapter we identify a knowledge gap as only very few clinical trials have explicitly focused on the effectiveness of CBT added to DBS in patients with therapy-resistant OCD. 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 to allow for the development of an algorithm and clinical guidelines for concomittant therapies to optimize treatment effects in OCD-DBS.

Although DBS has the attractive characteristics of reversibility and adjustability, it also incurs large capital costs and necessitates a large, expert multidisciplinary team to provide programs for patients and troubleshoot issues. DBS also commits patients to a lifelong implant, with subsequent battery replacements, which can be problematic in some disorders that affect young adults such as OCD.[58] Potentially, ablative therapies such as GVC avoid these risks and limitations, as it is typically characterized by a single radiosurgical procedure.[59] Indeed, the efficacy and safety profile of GVC and DBS have been found more or less to be equal in a recent meta-analyses.[60] Moreover, high frequency DBS as used in DBS is considered to have the effect of interrupting the information flow, comparable of the aim of lesioning procedures. Further, given the anatomical location of the target of GVC, the ventral ALIC, it may be hypothesized that both procedures may share the biological substrate of effective therapy. Nevertheless, as presented in **Chapter 3**, we were not able to replicate the association between implicated DBS tracts and clinical response in a subset of 8 refractory OCD patient treated with GVC. Furthermore, individual variation in sensitivity to radiation as exemplified by lesion volumes was observed in our cohort as well as other studies.[59] The absence of an identified biological substrate, the unpredictability of radiation sensitivity, and

the lack of studies with a high level of evidence foster our conclusion, despite its long history, that GVC may not *yet* be considered as an established treatment alternative for therapy refractory OCD.

Despite its limitations, we believe that findings as presented in this thesis strengthen the pillars upon which the identification of DBS as an established treatment rests; efficacy, safety and causality. Further developments in the field of treatment outcome measurements are warranted to determine the potential of DBS to revive treatment refractory OCD patients in society. Moreover, more insight into the differential effects of STN or ALIC stimulation and into individual anatomical variation of ALIC streamlines will allow for personalized therapy ultimately increasing the treatment efficacy.

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Chapter 10

Summary

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 1 - 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 concomittant 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.

Chapter 11

Impact and valorization

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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Chapter 12

Appendices

Samenvatting

De basis voor hedendaagse psychologische modellen van de obsessieve compulsieve stoornis (OCS) is de breed gedragen aanname dat ongewenste, opdringerige gedachten, beelden en impulsen bij de meeste mensen in de algemene bevolking voorkomen. Meestal kunnen personen op een adequate manier met deze gedachten, beelden of impulsen omgaan door het hanteren van geschikte coping mechanismen. Soms kunnen, volgens de cognitieve gedragstheorieën ontwikkelen deze opdringerige cognities zich via verschillende cognitieve processen tot klinisch relevante obsessies. Ten eerste, een persoon die vatbaar is voor OCS beoordeelt een opdringerige gedachte als zijnde een persoonlijke verantwoordelijkheid, of ervaart deze als bedreigend. Ten tweede, aangezien deze opdringerige cognities aanzienlijke spanning zullen veroorzaken, en wanneer meer gebruikelijke afleidingsstrategieën falen, zal die persoon een neutraliserende reactie ontwikkelen, hetzij openlijk, in de vorm van compulsief gedrag, of latent, in de vorm van gedachterituelen, die erop gericht zijn de angst- of paniekopwekkende effecten van de obsessie direct te verminderen. Het aangaan van deze neutraliserende activiteiten kan leiden tot een toename van de saillantie van de obsessie, wat dus leidt tot een toename van de opdringerige gedachte met als gevolg een toename van neutraliserende activiteiten, waardoor een vicieuze cirkel ontstaat. Het mag duidelijk zijn dat voor het complex van symptomen bij OCD geen individueel cortico-basale ganglia-thalamo-corticaal circuit verantwoordelijk is. In plaats daarvan is het aannemelijk dat meerdere anatomische parallelle fronto-striatale circuits betrokken zijn.
Verschillende interventies zijn effectief bij de behandeling van OCS, waaronder gedragstherapie, cognitieve therapie en cognitieve gedragstherapie (CGT). Bovendien is er veel bewijs voor het gebruik van selectieve serotonineheropnameremmers (SSRI's) en clomipramine, een tricyclisch antidepressivum, bij de behandeling van OCS. Vaak wordt een combinatie van CGT en medicatie gebruikt. 40-60% van de patiënten reageert niet op behandeling, wat wordt gedefinieerd als minder dan 25% vermindering van de Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score. Dit benadrukt de noodzaak van alternatieve behandelingsstrategieën, zoals diepe hersenstimulatie (deep brain stimulation, DBS) van subcorticale structuren (DBS) of gamma knife ventrale capsulotomie (GVC).
Het eerste deel van dit proefschrift is gericht op het identificeren van wittestofbanen, die geassocieerd zijn met klinische respons op DBS of GVC. OCS-patiënten presteren consequent minder goed op meerdere cognitieve domeinen. Het tweede deel van dit proefschrift is gericht op de neuropsychologische uitkomst van OCS-DBS om zo een cognitief patroon te identificeren dat geassocieerd zou zijn met de het therapeutisch effect van DBS, of (gedeeltelijk) zou helpen bij het verklaren van het werkingsmechanisme van OCS-DBS. Het derde deel is gericht op verschillende postoperatieve aspecten van (OCD)-DBS-patiënten, waaronder chirurgische en hardware-gerelateerde bijwerkingen van DBS en het beoordelen van de effectiviteit, timing en procedurele aspecten van CGT na DBS met als doel klinische aanbevelingen te doen.

Deel 1 - Anatomische overwegingen

Hoofdstuk 2 geeft een gedetailleerde klinische beschrijving en analyse van de behandelresultaten in een cohort van 8 refractaire OCS-patiënten behandeld met ventral capsule/ventral striatum (VC/VS) stimulatie. Primaire uitkomstmaten (Y-BOCS) en secundaire uitkomstmaten (depressieve symptomen, kwaliteit van leven en algemene gezondheid) werden retrospectief geanalyseerd. DBS-leads werden geregistreerd in een standaard stereotactische ruimte en een normatief connectoom werd gebruikt het neurale netwerk te identificeren dat geassocieerd is met klinische respons. Met een mediane stimulatieduur van 26 maanden, vertoonden patiënten een gemiddelde Y-BOCS-reductie van 10,5 punten, en een responspercentage van 63%. Modulatie van een vezelbundel die het anterieure been van het interne kapsel doorkruist (Anterior Limb of the Internal Capsule, ALIC) die de frontale regio's verbindt met de subthalamische kern (subthalamic nucleus, STN) en functioneel herkend als de hyperdirecte route, werd geassocieerd met response. Onze bevindingen tonen aan dat bij VC/VS-stimulatie hetzelfde neurale netwerk geassocieerd is met de klinische uitkomst als bij andere stimulatietargets, bijvoorbeeld de ALIC, de nucleus accumbens of de STN. Bovendien ondersteunen deze bevindingen de evolutie van het concept van optimale grijze stof stimulatie naar het moduleren van een functioneel netwerk.
Hoofdstuk 3 biedt een overzicht waarin we de bevindingen van connectomische studies en diepe hersenstimulatie-interventies integreren om een neuraal netwerk te karakteriseren dat vermoedelijk effectief is bij het verminderen van obsessies en compulsies. Recente ontwikkelingen, zoals geïllustreerd in **hoofdstuk 2**, suggereren dat veranderingen in netwerken, in plaats van lokale impact op het stimulatietarget, verantwoordelijk zijn voor verbetering van de obsessies en compulsies. Deze bevindingen worden gevoed door innovatieve methodologische benaderingen met behulp van hersenconnectiviteitsanalyse in combinatie met neuromodulatieve interventies. Een dergelijke zgn. 'connectomische' benadering voor neuromodulatie vormt een integraal geheel dat tot doel heeft optimale doelnetwerken te karakteriseren. Hiertoe onderzochten we verschillende toegepaste methodologieën resulterende in schijnbaar tegenstrijdige bevindingen met als doel observaties samen te voegen om gemeenschappelijke en diverse circuits voor de behandeling van obsessief-compulsieve stoornis te identificeren. Uiteindelijk stellen we een gemeenschappelijk verenigd netwerk voor dat - indien gemoduleerd door middel van corticale of subcorticale interventies - obsessief-compulsieve symptomen verlicht.
In **Hoofdstuk 4** analyseerden we pre- en postoperatieve MRI beelden van 8 patiënten die GVC ondergingen. Deze werden gebruikt om karakteristieken van GVC laesies te correleren met symptoomverbetering. En een normatief connectoom, gebaseerd op diffusie MRI tractografie werd gebruikt om netwerken te associëren met succesvolle laesies. Deze studie benadrukte de werkzaamheid van GVC bij patiënten met therapieresistente OCS. We waren niet in staat om specifieke wittestofbanen te identificeren die geassocieerd zijn met klinische respons, noch om de klinische uitkomst te voorspellen met behulp van eerder geïdentificeerde wittestofbanen in DBS, zoals die welke beschreven werden in **hoofdstuk 2**

en 3. Dit impliceert dat interindividuele anatomische variabiliteit, d.w.z., de . organisatie van wittestofbanen in het voorste lidmaat van de interne capsula, verklarend zou kunnen zijn voor de variabiliteit van de behandeling. De sterkste correlatie met symptoomverbetering werd gevonden voor een afname van het linker ventrale diencephalon volume (r=-0.83, p=0.039). Onze resultaten ondersteunen eerdere bevindingen dat zowel ablatieve als niet-ablatieve behandelstrategieën voor therapierefractaire OCS de frontostriatale netwerkactiviteit herstellen.

Deel 2 – Neuropsychologische overwegingen

In **Hoofdstuk 5** evalueerden we de cognitieve bijwerkingen en verkenden eventuele verklarende behandelingsmechanismen van DBS voor OCS door middel van een systematische review gecombineerd met een case-serie. EMBASE, PubMed/Medline, Psycinfo en de Cochrane Library werden systematisch doorzocht naar studies die neuropsychologische prestaties rapporteren voor en na DBS voor OCS. Zoekopdrachten werden voltooid tot november 2020. De opgenomen onderzoeken werden beoordeeld op studie-design en kwaliteit gebruik makende van kwaliteitsbeoordelingsinstrumenten van de National Institutes of Health (NIH). Voor de case-serie werden de neuropsychologische uitkomsten van zeven patiënten retrospectief beoordeeld. Veranderingen ten opzichte van baseline en laatste follow-up werden geanalyseerd en vergeleken met klinische verbetering. Vijf gerandomiseerde gecontroleerde onderzoeken en negen observationele onderzoeken met in totaal 171 patiënten werden gezamenlijk geanalyseerd. Variabele uitkomsten werden waargenomen op het gebied van aandacht en geheugen, executief functioneren en in het bijzonder cognitieve flexibiliteit. In de casusreeksen liet de Trail Making Test-ratio, die indicatief is voor cognitieve flexibiliteit, een significante afname zien, met een gemiddelde effectgrootte van 0,63. Hoewel individuele onderzoeken over het algemeen geen cognitieve achteruitgang rapporteren na DBS voor OCS, verhinderden de variabiliteit van de onderzoeksopzet en de talrijke verschillende cognitieve metingen een meta-analyse om de veiligheid en herkenning van een cognitief patroon te bevestigen waardoor de werkzaamheid van DBS voor OCS zou kunnen worden bepaald. Toekomstige, prospectieve studies zouden een gestandaardiseerde neuropsychologische beoordeling moeten bevatten die specifiek gericht is op de executieve functies en follow-up op langere termijn om de cognitieve veiligheid van de procedure aan te tonen en bij te dragen aan ons begrip van het werkingsmechanisme van DBS bij OCS.

Hoofdstuk 6 biedt een systematische review met als doel de werkzaamheid, timing en procedurele aspecten van postoperatieve CGT bij OCS-patiënten behandeld met DBS te onderzoeken. Na het starten met DBS hebben veel patiënten nog steeds medicatie en/of gedragstherapie nodig om aanhoudende symptomen en gewoontegedrag te behandelen. De klinische praktijk van het aanbieden van postoperatieve cognitieve gedragstherapie (CGT) varieert sterk en er zijn geen klinische richtlijnen voor deze aanvullende therapie. In deze

analyse hebben we 5 originele studies, een case series en drie reviews opgenomen. Slechts twee klinische onderzoeken hebben zich expliciet gericht op de effectiviteit van CGT toegevoegd aan DBS bij patiënten met therapieresistente OCS. Deze twee onderzoeken toonden beide de effectiviteit van CGT aan. Ze hadden echter een duidelijk ander ontwerp, zeer kleine steekproefomvang en verschillende manieren om CGT toe te dienen. Er kunnen daarom geen harde conclusies worden getrokken of aanbevelingen worden gedaan voor het aanbieden van CGT na DBS bij therapieresistente OCS. De effectiviteit, timing en procedurele aspecten van CGT toegevoegd aan DBS bij therapieresistente OCS zijn nauwelijks onderzocht. Voorlopig bewijs geeft aan dat CGT een bijkomend effect heeft bij OCS-patiënten die met DBS worden behandeld. Aangezien het totale behandelingseffect het gecombineerde resultaat is van DBS, medicatie en CGT, moeten toekomstige onderzoeken zo worden opgezet dat ze het effect van aanvullende therapieën bij OCS-patiënten die met DBS worden behandeld, kunnen kwantificeren. Alleen op deze manier kan informatie worden verzameld die zou kunnen bijdragen aan de ontwikkeling van een algoritme en klinische richtlijnen voor gelijktijdige therapieën om de behandelingseffecten bij OCS-patiënten die worden behandeld met DBS te optimaliseren.

Deel 3 – Postoperatieve aspecten

De introductie van DBS bij OCS brengt nieuwe uitdagingen met zich mee, zoals het op jongere leeftijd patiënten verbinden aan een levenslang implantaat. In **Hoofdstuk 7** hebben we patiënten geanalyseerd die tussen januari 2011 en juli 2020 DBS-gerelateerde procedures ondergingen met als doel om retrospectief bijwerkingen ('adverse events', AE's) te inventariseren. Van januari 2011 tot juli 2020 werden 508 DBS-gerelateerde procedures uitgevoerd, waaronder 201 implantaties van hersenelektroden bij 200 patiënten en 307 implanteerbare pulsgeneratoren (IPG)-vervangingen bij 142 patiënten. De gemiddelde follow-up tijd was 43 ± 31 maanden. Een univariate logistische regressieanalyse werd gebruikt om de voorspellende waarde van geselecteerde demografische en klinische variabelen te beoordelen. Bij 40 van de 200 patiënten (20%) kwamen chirurgische- of hardware-gerelateerde bijwerkingen na de eerste implantatie voor en ze verdwenen in alle gevallen zonder blijvende gevolgen. De meest voorkomende AE's waren postoperatieve wondinfecties (POWI's) (20/201, 9,95%) en problemen met littekenweefsel rond de extensiedraden van de DBS (wire-tethering) (5/201, 2,49%) gevolgd door defect hardware materiaal (4/201, 1,99%), huiderosie (2/ 201, 1,0%), pijn (1/201, 0,5%) leadmigratie (0,52%, 2/386 elektrodeplaatsen) en bloeding (0,52%, 2/386 elektrodeplaatsen). Het totale aantal AE's voor IPG-vervanging was 5,6% (17/305). Er werden geen chirurgische-, of patiëntgerelateerde risicofactoren geïdentificeerd voor POWI's of draad-tethering. Ernstige AE's, zoals een intracraniële bloeding, of AE's die chirurgische verwijdering of revisie van hardware vereisten, waren zeldzaam. Deze analyse bood geen ondersteuning voor eerdere studies, die suggereerden dan patiënten met nieuwe indicaties zoals OCS, epilepsie en TS vatbaarder zouden zijn voor

hardware gerelateerde AE's in vergelijking met PD-patiënten. In het bijzonder is agressieve behandeling vereist bij POWI's waarbij meerdere locaties betrokken zijn of wanneer een S. aureus wordt geïdentificeerd. Voor toekomstige benchmarking zou de ontwikkeling van een uniform rapportagesysteem voor chirurgische en hardware gerelateerde AE's bij DBS-chirurgie nuttig zijn.

Hoofdstuk 8 geeft een kostenanalyse van de behandelingsopties van een van de meest verontrustende hardware-gerelateerde complicatie van DBS, infectie. Deze infecties kunnen worden behandeld met antibiotica of met verwijdering van de geïnfecteerde hardware gevolgd door re-implantatie. In onze ervaring is het succes van antibiotische therapie ongeveer 50%. In deze studie hebben we de kosten onderzocht van het behandelen van de infectie met alleen antibiotica met het risico van een operatie wanneer dit niet lukt versus onmiddellijke verwijdering gevolgd door re-implantatie. De kosten van de behandeling van een geval van DBS-hardware-infectie met onmiddellijke IPG-vervangende chirurgie waren € 29.301 en € 9499 voor succesvolle antibioticabehandeling. Voor antibioticabehandeling gevolgd door IPG-vervangende chirurgie waren de totale kosten € 38.741. Behandeling met alleen antibiotica was succesvol in 44% (4/9) van de geïncludeerde gevallen van DBS-infectie, resulterend in een gemiddelde behandelingskosten per patiënt van € 25.745. Pogingen om DBS-hardware-infecties in eerste instantie met antibiotica op te lossen, verlaagden de behandelingskosten met 12,1%. Behandeling met antibiotica met het risico van een latere verwijdering wanneer niet succesvol was een waardevollere strategie in termen van kosten in vergelijking met onmiddellijke chirurgische interventie in geval van hardware-gerelateerde infecties bij DBS-operaties.

De algemene discussie in **hoofdstuk 9** is opgedeeld in twee delen. In het eerste deel zullen gemeenschappelijke thema's binnen en tussen de delen van dit proefschrift grondiger worden besproken in het licht van het identificeren van neurochirurgie als een geaccepteerde therapie voor refractaire OCS. In het tweede deel zal een neuro-computationeel model van OCS worden geïntroduceerd, inclusief een afbakening van zijn anatomische onderdelen, zoals geïdentificeerd in dit proefschrift, binnen de cortico-basale ganglia-thalamo-corticale feedbackloop omgeving.

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Curriculum Vitae

Tim Antonius Martinus Bouwens werd op 27 november 1988 geboren in Heerle, Noord-Brabant. In 2001 startte hij met het tweetalig VWO aan het Jan Tinbergen College te Roosendaal. In 2005 ontving hij een studiebeurs, waardoor in 2005 het VWO onderbroken werd voor een eenzijdige uitwisseling naar Koryoo Kokkoo High School Fukuoka, Japan. In 2008 begon hij met zijn geneeskundestudie aan het Erasmus Medisch Centrum, te Rotterdam. Tijdens zijn geneeskundestudie raakte hij betrokken bij verschillende onderzoeksprojecten met als centraal thema het glioblastoom, onder supervisie van dr. H. Al-Khawaja, dr. M.L.M. Lamfers, dr. L. Trouw (LUMC), prof. dr. P. van der Spek, prof. dr. C.M.F. Dirven en prof. dr. J.M. Kros. Hij ontving een subsidie van de Koninklijke Nederlandse Akademie van Wetenschappen voor buitenlands congresbezoek, en een poster-award tijdens de '14th European Meeting on Complement in Human Disease, Jena, Germany' voor zijn werk met betrekking tot complementactivatie in het glioblastoom. Gedurende zijn studie ontwikkelde hij een bijzondere interesse in de anatomie, wat tot uiting kwam als lid van 'het snijzaalteam' en zijn betrokkenheid bij het 'Erasmus Anatomy Research Project', onder supervisie van prof. dr. G.J. Kleinrensink, waarvan hij later respectievelijk teamleider en voorzitter werd. Na zijn opleiding geneeskunde startte hij in 2015 als arts-assistent neurochirurgie in het Slotervaart Ziekenhuis te Amsterdam. Hij begon in 2016 aan de opleiding tot neurochirurg met als opleiders prof. dr. van Overbeeke, dr. Ter Laak en dr. Van Aalst in het Maastricht Universitair Medisch Centrum. Gedurende de opleiding werkte hij van 2009 tot 2021 aan de 'School for Mental Health & Neuroscience' van het Maastricht Universtair Medisch Centrum aan het onderzoek wat heeft geleid tot dit proefschrift. Dit gebeurde onder supervisie van dr. Ackermans, prof dr. Y. Temel and prof. dr. A. Leentjens. Hij is tevens AIOS lid van de sectie functionele neurochirurgie van de Nederlandse Vereniging voor Neurochirurgie. Tim ontmoette zijn liefhebbende vrouw Madelon in de romantische ambiance van de snijzaal van het Erasmus MC. In 2014 zijn zij getrouwd. Zij hebben samen 3 dochters: Julia, Roos en Nova.

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