On connecting dots

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FROM IMAGING TO STIMULATING THE OBSESSIVE-COMPULSIVE BRAIN

Samantha Baldi

Doctoral Thesis

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CHAPTER 1

GENERAL INTRODUCTION & OUTLINE OF THE THESIS

When at the airport, repeatedly checking to carry the necessary documents. When leaving the house, doubting that the light of the bathroom was switched off. When being on the tram, feeling that seats and handles are gross, dirty, not to be touched. When reorganizing the closet, feeling the need of categorizing every item by color, material, occasion of use.

These are just a few examples of common experiences, likely shared by the readers of these pages. In the present times, it is relatively easy to label these feelings, and consequent behaviors, as *"being a little OCD"*, a statement sometimes intended as a synonym of being precise, meticulous and thorough. OCD, or Obsessive-Compulsive Disorder, has transformed into an adjective for everyday use, with which everyone is to some extent familiar.

Although OCD-like experiences can be recognized as common yet sporadic occurrences affecting the general population, OCD is amongst the most debilitating psychiatric conditions. Affected individuals spend a considerable amount of time afflicted by intrusive thoughts, images or impulses, rigidly performing specific mental or behavioral rituals as a response (1). OCD comes with strong, uncontrollable anxiety and fear that terrible events might occur if not able to control certain feelings and behaviors. Patients are consequently limited in many aspects of their life, struggling to complete ordinary tasks, likely becoming socially isolated, unable to work or live independently (2).

The neuroscientific approach to studying OCD has evolved in parallel with the increasing awareness that understanding and treating OCD symptoms is not straightforward. Identifying a single, putative cause that is able to explain every clinical case is admittedly unrealistic. Similar to many other psychiatric disorders, OCD rather stems from the complex interplay between various forms of biological or psychological vulnerability (e.g., genetics) and environmental/circumstantial factors (e.g., traumatic events), potentially resulting in new or strengthened forms of dysfunction that either cause the emergence of, or maintain, phenotypic manifestations. While some dysfunctional mechanisms might be more specific to OCD, some others belong to broader concepts that interact with psychopathology in general. Whereas neuroscientific research has traditionally focused more on the first aspects, the field has recently developed a strong interest in identifying trans-diagnostic elements of the clinical and biological manifestations of different psychiatric disorders. The first chapters of this thesis (**Chapter 2, 3, 4**) align with this trend, focusing on alterations in the circuitries of the brain.

As with conceptualizing the brain basis of OCD, a "one size fits all" approach is equally inappropriate when evaluating treatment. According to standard guidelines, a newly diagnosed patient is presented with psychotherapy interventions, comprising

exposure to triggering stimuli or situations while preventing the associated compulsions, and cognitive re-structuring of dysfunctional beliefs. In some cases, combination with pharmacotherapy is beneficial (3), although the search of an effective medication can be excruciatingly long. Despite optimal use, however, these standard approaches are not effective for every patient. Up to an estimated 30-40% remains highly symptomatic and needs alternative treatments (4), available in the form of neuromodulation interventions. Generally, these are more costly, invasive, or come with associated risks, and are thus only accessible to very severe patients that failed a multitude of standard attempts. Further, there are currently no guidelines on how to tailor these interventions on the individual patient. The second part of this thesis first focuses on a few aspects related to the use of invasive brain stimulation for the treatment of OCD (**Chapter 5, 6**). Finally, we evaluate a potential approach for a personalized, non-invasive neuromodulation intervention (**Chapter 7**).

The present chapter provides the necessary background to understand the chapters that will follow. First, we give an overview of what OCD entails, and of the imaging and stimulation techniques that were used to conduct the studies presented. We then conclude with describing the aim and outline of the present thesis.

1. On obsessive-compulsive disorder

OCD affects an estimated 50 million people worldwide, nearly 3% of the general population (5), ranking as the fourth most common psychiatric disorder (6) and amongst the twenty most debilitating diseases (7). Current diagnostic manuals identify OCD by the combined or isolated presence of obsessions (i.e., recurrent, intrusive thoughts, images or impulses perceived as unwanted and often triggering marked anxiety) and compulsions (i.e., repetitive mental or behavioral rituals that the individual feels obliged to perform in response to an obsession or following rigid rules) (1). Compulsions are specifically aimed at preventing a feared event or situation from happening or reducing the elicited anxiety, although they might over time become habits, automatically elicited by certain stimuli rather than obsessive thoughts (8). Often, these acts are not linked by any logic with what they are designed to neutralize or, if they are, they are overtly excessive (1).

OCD manifests heterogeneously across individuals, for example varying in the frequency, intensity and content of obsessions and compulsions. Accordingly, distinct symptom dimensions have been identified, categorizing temporally and cross-culturally stable themes of manifesting symptoms (9). These include for example symmetry obsessions (e.g., need for things to be perfect) and associated counting, ordering or arranging compulsions (e.g., evening up or aligning objects); forbidden or blasphemous

thoughts like aggressive, sexual or religious obsessions (e.g., thoughts about stabbing someone, sexual acts with children, committing immoral behaviors) and associated compulsions (e.g., excessive praying, overanalyzing one's behavior, avoiding triggering objects or situations); and obsessions about contamination (e.g., becoming ill) with consequent cleaning compulsions (e.g., hand washing). Notably, in the majority of cases multiple dimensions co-occur in the same patient (1).

As mentioned above, most people might recognize themselves in a few of these occurrences. To help distinguish innocuous, occasional experiences from a full-blown disorder, diagnostic criteria state that obsessions and compulsions must be time-consuming (i.e., take more than 1 hour per day), and must cause clinically significant distress or impairment in different life domains (1). If left untreated, OCD often follows a chronic course with fluctuating symptoms severity, and is generally associated with a marked reduction in quality of life, increased financial burden and mortality (10, 11).

This complex, disabling clinical profile is often aggravated by co-occurring comorbidities. Studies report many adults with OCD (up to 50-80%) to have a lifetime diagnosis of at least one anxiety disorder (e.g., panic disorder, social anxiety, generalized anxiety disorder, specific phobia) or, most often, major depressive disorder (1, 5, 12). Comorbidity with substance use disorders, eating disorders, tic disorders, or trichotillomania is also frequently documented (1, 5).

OCD is characterized by a bimodal age-of-onset distribution, peaking in either late childhood (9-11 years) or early adulthood (19-25 years) (13), and differences in the etiological, phenotypical and treatment makeup of early- vs. late-onset OCD have been reported (14-16). Prevalence rates are higher for male children, while some evidence has suggested a slightly higher risk for adult females to develop the disorder (1, 17). Generally speaking, OCD however most commonly gradually arises before 35 years of age, emerging later than most comorbid anxiety disorders but generally preceding the occurrence of depressive episodes (1).

2. On imaging the brain

As mentioned in the general introduction, the path leading to and maintaining obsessions and compulsions is complex and involves different etiological factors interacting with each other. To understand why individuals might experience OC symptoms, attention should be given to studying genetics, environment, cognition, physiology, brain circuitries, and neurotransmitter systems. The current thesis primarily focuses on studying the circuitries of the brain, using different magnetic resonance imaging (MRI) techniques.

By means of strong magnetic fields, magnetic field gradients, radio-frequency waves and complex reconstruction algorithms, MRI allows non-invasively creating 3-dimensional detailed images of nearly any structure and organ inside the body. A plethora of different acquisition protocols exists that is able to capture different properties of the biological signal under investigation, leading to images with different contrasts, different resolutions, different dimensions and, most importantly, conveying different types of information. When imaging the brain, MRI sequences can deliver information about its anatomy (structural MRI), specific properties of white-matter (diffusion MRI), or about its function (functional MRI), at rest or when complying with the instructions of a task (18). In the research context, the use of MRI has allowed great advances in the understanding of the neural bases of normal and abnormal brain function, and has contributed to the recognition of psychiatric syndromes as "brain disorders".

The approach on how to investigate the brain basis of psychopathology has changed considerably over time. For many years, neuroscientific studies aimed at unravelling etiological and pathophysiological mechanisms by looking at alterations in specific regions of the brain, based on leading theories or building upon the first emerging evidence. Additionally, effort was primarily devoted to identifying elements that would be disorder-specific, in the attempt to find a brain equivalent of clinical diagnostic categories. In this first era of neuroscience research, OCD has been convincingly linked to alterations in the cortico-striatal-thalamo-cortical (CSTC) loops of the brain (19, 20). As a general organizing structure, these loops originate from specific territories within the frontal cortex, projecting to distinct areas of the striatum and then reaching the thalamus, via the direct and indirect pathways through the basal ganglia. From the thalamus, projections then travel back to the frontal territories where each loop started, exerting a net excitatory or inhibitory effect on cortical activity and engagement (20). Different parts of the circuitry subserve different functions, and initially three main loops were identified: a dorsal cognitive circuit (for executive functions such as working memory, planning), a ventral cognitive circuit (for response inhibition) and an affective circuit (for reward processing) (20). The literature relating dysfunctional CSTC circuits to the pathophysiology of OCD is extensive and includes several lines of evidence, ranging from the early positron-emission tomography studies demonstrating metabolic abnormalities to structural, functional and lesion studies, all pointing to the critical involvement of various components of the circuits (21). This model has initially served a well-defined neurobiological conceptualization of OCD, and has greatly influenced the first applications of invasive and non-invasive neuromodulation treatments (detailed below).

However, the neuroscience field has gradually acknowledged that attempting to identify dysfunctions in a few, circumscribed regions is too simplistic: different

circuitries in the brain are indeed more integrated than initially thought, linked together by a complex ensemble of connections, giving rise to articulated, precisely coordinated dynamics that support efficient behaviors (22). Thanks to the development of novel, advanced MRI and processing methods, neuroscientific studies have started to focus more and more on the networks of the brain, defining and boosting the field of connectomics, i.e., the study of the properties of structural, functional or effective connectivity between brain regions (23). Structural connectivity refers to the anatomical connections linking a set of neural elements, generally studied reconstructing white-matter fiber tracts by means of diffusion MRI. Functional connectivity refers to the statistical dependence of neural elements, generally derived from time series observations that, in the context of neuroimaging, are acquired using functional MRI methods. Although useful, these measures do not allow any inference to be made about one region causally influencing another via direct or indirect connections: currently available methods do not allow directionality of white-matter tracts to be disentangled, while functional connectivity relies on highly time-dependent statistical relationships that do not imply causality (24). Although not addressed in the current thesis, effective connectivity on the other hand tries to describe directed causal links between elements of a network, via generation of mechanistic models explaining how one element influences another (25).

Following the first decades of research centered on CSTC loops dysfunction, neuroscientific studies on OCD neurobiology thus refocused to the brain as a whole, leading to the discovery of several other brain regions and widespread networks potentially playing a role, expanding the original, relatively circumscribed neuroanatomical model of the disorder. A neurocircuit-based taxonomy of OCD has been recently suggested, introducing the idea that different clinical profiles might be better explained by dysfunction in one brain system or another (26). For example, attention has been devoted to the fear, fronto-limbic and sensorimotor networks (26); to key brain regions densely connected with cortical and subcortical nodes, like the cingulum, insula or anterior cingulate cortex (27, 28); to large-scale intrinsic networks in interaction with each other (29); or to properties of whole-brain network organization and topology (30-32).

Notably, adopting this approach across different fields highlighted many similarities in the brain alterations of different psychiatric disorders, questioning the original way of focusing on the brain specificity of diagnostic categories. Initiatives have been put in place that rather pose the accent on alterations in major functional domains and critical environmental aspects that might trans-diagnostically underlie psychopathology (33). The neuroimaging studies constructing the current thesis align with the outlined evolution of the field, focusing on the structural and functional

connectivity linking circuitries of the brain, and investigating elements that might likely but not solely be linked to OCD brain pathology.

3. On stimulating the brain

According to the International Neuromodulation Society, therapeutic neuromodulation refers to the "alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body" (34). Neuromodulation approaches range from invasive (e.g., spinal cord stimulation, deep brain stimulation, intrathecal drug delivery) to non-invasive techniques (e.g., transcutaneous nerve stimulation, transcranial magnetic stimulation (TMS), transcranial direct or alternating current stimulation), which are successfully used to treat a number of different conditions. Among this vast range, in the present thesis we focus on the brain stimulation techniques that are currently used and continuously investigated for the treatment of refractory OCD: DBS as invasive, and TMS as non-invasive options.

DBS is a neurosurgical technique, introduced in the late 1980s to treat severe tremor (35). The DBS system comprises three main elements: the lead (i.e., a coiled wire with multiple electrode contacts at the tip), connected via an extension (i.e., an insulated wire running below the skin down the side of the neck) to an implantable pulse generator (IPG), placed subcutaneously under the clavicle or in the abdomen. The IPG is battery-powered and, when turned on, generates high-frequency electrical pulses that, traveling through the extension, are then discharged via the electrode contacts at the specific brain location where the lead is implanted. The DBS leads are inserted bilaterally in the brain via the use of a stereotactic frame and stereotactic coordinates, while the patient is either awake or asleep. Some days later, the extension and the IPG are implanted under general anesthesia.

As with every surgical procedure, DBS comes with a number of associated risks, including bleeding, infections, blood clots and reactions to anesthesia. Specific to the DBS system, patients might require additional surgery upon breakage of the extension wire or infection/mechanical failure of the implanted device. However, despite the risks inherent to the procedure itself, DBS is generally considered safe and well tolerated, with considerable advantages compared to ablative surgery, an irreversible procedure originally used to treat refractory OCD (36). First, DBS is reversible, as any elicited change is (generally) dependent on the stimulator being active, and can thus be reversed by either removal or shutdown of the IPG. Second, DBS is adjustable, as several parameters can be tuned to optimize the effects of stimulation while reducing undesired side-effects. This optimization phase can however be a lengthy procedure, lasting up to several months.

DBS has been first introduced as treatment for refractory OCD in 2009, receiving approval as humanitarian device exemption from the US Food and Drug Administration (FDA) and a Conformité Européenne (CE) mark (37). Since then, several open-label and randomized controlled trials have accumulated to evaluate its effectiveness and impact, with literature reporting more than 300 operated patients worldwide (38). However, compared to the treatment of neurological disorders (e.g., Parkinson's disease), DBS is still limitedly used in psychiatry (39). OCD patients are indeed only considered eligible upon meeting stringent criteria for treatment refractoriness, implying the failure of appropriate trials of psychotherapy (i.e., at least 20 hours including exposure and response prevention) and pharmacotherapy (i.e., two trials with selective serotonin reuptake inhibitors and one trial with clomipramine at maximum doses for at least 12 weeks). Even then, not all refractory patients undergo surgery. Although many reasons should be considered (39), the preference towards less invasive options plays a role for both treating psychiatrists and patients.

TMS is a non-invasive form of brain stimulation, originally restricted to the diagnosis of neuro-motor disorders but later extensively researched for its antidepressant effects. The TMS device comprises two main elements: a coil (i.e., copper wired in one or more touching loops), connected to a stimulator. During TMS application, the stimulator sends high-voltage current pulses to the coil, which is held tangentially to the patient's head at a specific location. The moving electric field generates a magnetic field that penetrates the skull, and in turn produces an electrical current sufficiently fast and strong to depolarize the underlying neural elements, elicit action potentials and trigger processes of synaptic plasticity (40). Different types of coils elicit different magnetic field patterns. Standard TMS coils (e.g., figure-of-eight) allow delivering highly focal stimulation pulses to a targeted area, however only at an appreciated depth of maximum 2-3 cm under the skull. On the other hand, more recently developed coils (e.g., H1 deep coil, double-cone coil) have been specially built to reach deeper areas (~3-5 cm depth), at the expense of reduced focality of stimulation (41). The type of coil can then be combined with the choice of several other parameters, such as the frequency and intensity of the delivered pulses, thus giving rise to a wide range of possible stimulation protocols, with differential effects on cortical excitability.

Side-effects of TMS are primarily mild to moderate and tend to disappear shortly after the end of a session, including for example headache, scalp discomfort at the site of stimulation, and tingling or twitching of facial muscles. Severe adverse events are rarely reported, and only a few instances of seizures, mania or hearing loss have been documented (42-44).

TMS first received FDA approval for the treatment of depression in 2008, delivering high-frequency stimulation over the left dorsolateral prefrontal cortex

(dlPFC) in treatment-resistant patients (45). Since then, many studies have researched its value for treating other psychiatric disorders (44). In OCD, several combinations of stimulation targets (e.g., bilateral or unilateral dlPFC, supplementary/pre-supplementary motor area (SMA), orbitofrontal cortex) and protocols (high frequency, low frequency) have been investigated using standard TMS coils (46-48). A recent network meta-analysis of 21 studies showed comparable efficacy across protocols, amounting to four points more decrease in symptoms severity scores as compared to sham TMS. When contrasting each stimulation target/protocol combination, results highlighted the equal superiority of low frequency bilateral pre-SMA, high frequency bilateral dlPFC and low frequency right dlPFC stimulation (46). However, the small studies included, and the limited number of trials for each stimulation target/protocol combination, impede definitive conclusions on the relative virtue of different options. Thus, despite positive results emerging, the decision on where to stimulate is still to some extent experimental. The use of deep coils is on the other hand more clearly regulated. In 2019, a high-frequency TMS protocol stimulating the dorsal anterior cingulate cortex with an H1 or double-cone coil received FDA clearance for the treatment of refractory OCD (49, 50). However, the lack of replication across wider cohorts and tailoring on individual patients is still recognized as a general shortcoming, stimulating further research into alternative approaches.

The use and understanding of both invasive and non-invasive neuromodulation have followed the outlined evolution of the imaging field. When these methods started being used in the context of OCD, stimulation sites for both invasive and non-invasive applications were chosen among those areas critically participating in the CSTC loops. When evaluating the mechanisms of action then leading to symptoms improvement, both DBS and TMS were believed to work primarily by acting focally on the pathological activity of the area of stimulation. However, with the shift in emphasis on connected networks rather than isolated regions, greater attention has been concomitantly placed on the remote, distal effects of the elicited local changes. Studies have started to show that e.g., DBS implanted in the nucleus accumbens normalizes altered functional connectivity between the nucleus accumbens and the frontal cortex (51), or that TMS success for treating depression might depend on the functional connectivity of the dlPFC with the subgenual cortex (52). Thus, neuromodulation studies are now generally, as well as in the present thesis, developed under the hypothesis that the modulation of connected networks might in fact be the key element to relieving obsessions and compulsions, and that this knowledge can be used to guide the selection of an appropriate stimulation target.

4. Aim and outline of the thesis

An overarching aim in psychiatry research is to maximize treatment success, by designing and assigning interventions that fit, at least to some extent, each individual patient. In regard to OCD, optimal use of psychotherapy and pharmacotherapy effectively relieves symptoms in the majority of patients. Yet, a non-negligible portion of individuals fails to respond to these treatments and becomes eligible for neuromodulation interventions. Although these procedures are administered with a certain success, still many uncertainties surround their application. Particularly, it is not yet clear how their use can be tailored on the individual patient. Considering the heterogeneity in both phenomenology and neurobiology, the need for more personalized interventions is specially pressing for OCD patients.

The present chapter outlines the evolution that the fields of neuroimaging and consequently also neuromodulation underwent. We describe how attention shifted from looking at a few, circumscribed brain regions to considering widespread connected networks and from a disorder-specific perspective to one connecting dots across mental disorders. These acquired notions point to several questions that are relevant to be posed in the endeavor to personalized brain stimulation treatment: What are effective patient-clustering approaches? Do they rely on OCD specific or non-specific, trans-diagnostic markers? What do neuromodulation interventions imply, and can we devise new, personalized applications?

In its different parts, the present thesis aims to address a few, at times preliminary, considerations relating to these broader questions, which unfold as herein described.

PART 1: TRANS-DIAGNOSTIC CONSIDERATIONS ON OCD

Any potentially successful treatment stratification relies on the identification of effective patient-clustering approaches. Over the years, several have emerged that rely on either clinical or brain-based OCD-specific characteristics (26). The neuroscience field has however acknowledged the possibility that such clustering approaches might not necessarily lie within the boundaries of diagnostic categories. Rather, mental health problems might be better framed in terms of varying alterations in major psychological/biological systems, which then give rise to varying symptomatology (33). Unravelling the constituents of these systems first, and understanding how these systems are affected across patients (and commonly used diagnostic categories) then, is believed to ultimately lead to better prevention, diagnosis and treatment (33). Accordingly, in the first part of this thesis, we used different approaches to investigate psychological (**Chapter 2**), neural (**Chapter 3**) and environmental (**Chapter 4**) elements that might

likely but not solely be linked to OCD pathology. Importantly, when employing neuroimaging methods, we focus on regions of the brain in connection with each other. More specifically:

In **Chapter 2,** we analyze the neural basis of the single vulnerability factor most consistently associated with psychopathology: neuroticism (i.e., the tendency to experience negative affect, especially during exposure to stress) (53). In regards to OCD specifically, studies suggest moderate to high genetic correlations between neuroticism and some OC symptom dimensions (54-56), and higher levels of neuroticism in OCD patients (57-60), with a few results of a positive association with symptoms severity (61, 62), and a negative association with remission rates (63, 64). Despite the abundance of studies linking neuroticism to psychiatric symptoms, there is little comprehensive knowledge on the biological basis of this multifaceted construct, however necessary to validate it as a potential screening, etiologically informative tool. In Chapter 2, we characterize the multimodal brain correlates of cross-sectional and longitudinal measures of neuroticism in a large, population-based sample, investigating its associations with task- and resting-state functional, structural, and diffusion-weighted MRI.

In **Chapter 3,** we explore the link of a potential trans-diagnostic brain marker to OCD neurobiology. Starting from schizophrenia, and later extending to a wide range of psychiatric and neurological conditions, numerous studies highlighted common anomalies in a natural attribute of neural organization and function: rich-club organization. Rich-club organization refers to the property of topologically central regions of the brain to establish strong and numerous connections between them, enabling information to be integrated quickly and efficiently (65). In light of the limited available evidence on whether these alterations characterize OCD as well, in Chapter 3 we investigate rich-club organization in a sample of unmedicated OCD patients and their unaffected first-degree relatives.

In **Chapter 4,** we comment on the potential impact of an environmental factor specific to the period during which this thesis was constructed: the COVID-19 pandemic. In a time when sanitizing and social distancing measures have been heavily enforced on everyone, we wondered whether individuals with pre-existing obsessions about viruses and hygiene could be particularly vulnerable to an increase in symptoms severity. In Chapter 4, we review the available literature on the effects of strict hygiene measures imposed during the first wave of the pandemic on the symptoms of OCD patients, particularly those concerned by contamination and washing rituals.

PART 2: CRITICAL CONSIDERATIONS ON BRAIN STIMULATION TREATMENT

Maximizing treatment success and developing personalized interventions also imply in-depth knowledge of currently used applications and their mechanisms of action. In the context of OCD, invasive brain stimulation in the form of DBS is reserved to severe, refractory patients that failed to respond to standard therapeutic approaches. Many studies have accumulated thus far, demonstrating the efficacy of DBS in relieving obsessions and compulsions (38). However, its invasiveness demands that great care is placed on evaluating all possible caveats related to its application. Accordingly, in the second part of this thesis, we start with evaluating aspects related to DBS that might intendedly or unintendedly impact the symptoms and life of the patients (**Chapter 5, 6**). We then move on to considering non-invasive options, focusing on the use of TMS. In OCD, positive findings have emerged (46), although there is still uncertainty on the best stimulation target and protocol to use. As previously outlined in this chapter, it is now recognized that the modulation of connected networks might be the key mechanism to improve clinical symptoms. In the last chapter of this thesis, we explore how this knowledge can be used to guide the selection of a stimulation target in an individualized manner, assessing the implications of such procedure on different brain networks (**Chapter 7**). More specifically:

In **Chapter 5,** we systematically investigate the clinical effects of DBS that might in fact not be due to stimulation of the brain itself. Non-intervention-related effects have long been recognized in an array of medical interventions, to which surgical procedures are no exception (66-68). While placebo and micro-lesion effects have been demonstrated in DBS for major depression and Parkinson's disease (69-71), systematic investigations for OCD are lacking. In Chapter 5, we quantify the improvement in OC symptoms that followed a period where stimulation was inactive, by means of an individual patient data meta-analysis of published randomized controlled trials.

In **Chapter 6,** we characterize a wide variety of positive and negative experiences associated with DBS treatment, beyond specific improvements in OCD core symptoms. Success of DBS is generally assessed as a percentage reduction in symptoms severity, although it is known that the impact of the procedure extends well beyond (72, 73). Yet, only a few studies focused on characterizing the whole realm of DBS-related experiences in OCD patients (72, 73). In Chapter 6, we categorize the experience and

welfare of operated patients and their relatives in their very own perspective, by means of qualitive interview and analysis methods.

In **Chapter 7,** we investigate the feasibility of modulating non-invasively with TMS deep-brain nuclei of key relevance to OCD pathology. Harnessing the well-evidenced remote effects of cortical stimulation (74-77), we use individual structural connectivity patterns linking these deep-brain nuclei to the cerebral cortex to define accessible TMS targets. In a proof-of-concept study with healthy volunteers, we investigate TMS-induced changes in the functional connectivity networks of the remote regions that we aimed to target, discussing the potential relevance of these effects for OCD treatment.

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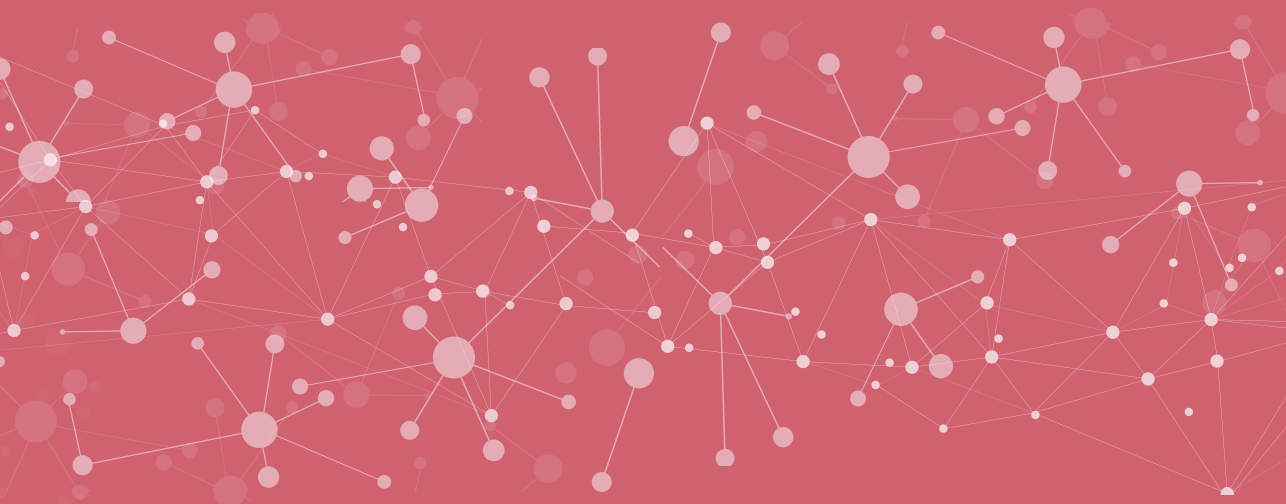
PART 1



TRANSDIAGNOSTIC CONSIDERATIONS ON OCD

THIS CHAPTER IS EMBARGOED ON REQUEST

CHAPTER 2

MULTIMODAL BRAIN CORRELATES OF NEUROTICISM: DISTINCT AND OVERLAPPING CONTRIBUTIONS OF DEPRESSIVE AND ANXIOUS TRAITS

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Manuscript in preparation

CHAPTER 3

ABNORMAL WHITE-MATTER RICH-CLUB ORGANIZATION IN OBSESSIVE-COMPULSIVE DISORDER

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Abstract

Rich-club organization is key to efficient global neuronal signaling and integration of information. Alterations interfere with higher-order cognitive processes, and are common to several psychiatric and neurological conditions. A few studies examining the structural connectome in obsessive-compulsive disorder (OCD) suggest lower efficiency of information transfer across the brain. However, it remains unclear whether this is due to alterations in rich-club organization. The structural connectome of 28 unmedicated OCD patients, 8 of their unaffected siblings and 28 healthy controls was reconstructed by means of diffusion-weighted imaging and probabilistic tractography. Topological and weighted measures of rich-club organization and connectivity were computed, alongside global and nodal measures of network integration and segregation. The relationship between clinical scores and network properties was explored. Compared to healthy controls, OCD patients displayed significantly lower topological and weighted rich-club organization, allocating a smaller fraction of all connection weights to the rich-club core. Global clustering coefficient, local efficiency and clustering of non-rich club nodes were significantly higher in OCD patients. Significant three-group differences emerged, with siblings displaying highest and lowest values in different measures. No significant correlation with any clinical score was found. Our results suggest weaker structural connectivity between rich-club nodes in OCD patients, possibly resulting in lower network integration in favor of higher network segregation. We highlight the need of looking at network-based alterations in brain organization and function when investigating the neurobiological basis of this disorder, and stimulate further research into potential familial protective factors against the development of OCD.

1. Introduction

Obsessive-compulsive disorder (OCD) is a severe psychiatric condition affecting 2-3% of the population world-wide, characterized by the combined or isolated presence of intrusive, recurrent thoughts, and associated repeated behaviors or mental rituals (1). Despite the abundance of evidence that has accumulated in the last decades, the exact neurobiology of OCD remains elusive; neuroanatomical models attempting to identify dysfunction of one or a few isolated brain regions are labelled as too simplistic, and it has long been recognized that looking at networks is the key (2). Graph-theoretical analyses of magnetic resonance imaging (MRI) data have proven valuable to understanding how information is integrated and communicated throughout the brain as a complex network, and have been widely employed to study several neurological and psychiatric conditions (3, 4).

In the normal functioning brain, spatially and functionally distinct regions exchange information quickly and efficiently, facilitating cognitive and behavioral responses appropriate to the environmental demands. Key players in this process are network hubs, regions that display high connectivity to the entire network, but are first and foremost densely interconnected with each other. This ensemble of connections forms a 'rich-club' within the brain, a high-capacity structural core that allows information to travel across distant regions that would hardly communicate otherwise (5). Rich-club connections have been mainly characterized by macroscopic white-matter connections (5, 6), although studies have also linked structural and functional rich-club organization with each other (7-9). Regions belonging to the rich-club have been shown to span all major resting-state networks (RSNs), and to participate in a large proportion of inter-RSNs connections (7). For this reason, the rich-club is regarded as the anatomical substrate for efficient communication across distant and/or segregated functional systems (7), argued to significantly contribute to global neural integration (5, 9, 10) and healthy brain function (11, 12). Given its prominent role, alterations in rich-club organization are believed to interfere with higher-order cognitive processes, leading to behavioral dysfunction. Such alterations are reported for several neurological and psychiatric conditions, including Alzheimer's disease (13), Parkinson's disease (14), schizophrenia (15), major depression disorder (16), autism spectrum disorder and attention-deficit/hyperactivity disorder (17).

A few studies examining white-matter networks in OCD suggest altered efficiency of information transfer across the brain (18-21). One study reports lower global and regional efficiency in OCD patients, predominantly within fronto-striatal and fronto-parietal networks (18). Another study points to a cluster of lower connectivity comprising temporo-limbic, insular, orbitofrontal and striatal regions. Their analysis of

graph measures highlights local alterations of mainly temporo-limbic regions, with indications of lower efficient connectivity of the left amygdala in particular (19). Remarkably, neither of these studies have investigated whether the reported decrease in efficiency of information transfer could relate to alterations in the rich-club organization of the brain. An attempt in this direction has been made recently by Zhou et al (2021), who show in contrast with findings above, higher global efficiency and higher rich-club organization and rich-club connectivity in OCD patients. The authors suggest that long-distance information integration and transmission capacity might be enhanced, potentially as a result of compensatory mechanisms (20). These results have however not been replicated by Peng et al (2021), who report lower rich-club organization and rich-club connectivity in OCD patients. Their findings of similar alterations in a group of unaffected first-degree relatives support altered rich-club organization as a candidate vulnerability marker of OCD (21).

The thorny problem of connectome-based studies is the myriad of methodological choices that stand between the construction of the network and the implementation and interpretation of graph measures. Contradicting findings are often blamed on the technical diversity of the study that generated them, rarely questioning the true biological validity of what is being explored. However, when there is no gold standard set out to follow, and each technical choice has its own pro and counterarguments, the scientific reliability of any result lies within their stability and replicability across a variety of methodological nuances. The limited and contradicting findings available to date do not suffice for a clear understanding of the rich-club phenomenon in this patient population, but more research is clearly needed.

The present study adds to the discussion and investigates rich-club organization and rich-club connectivity as potential markers of OCD, by using probabilistic tractography to reconstruct the white-matter network of a group of unmedicated OCD patients. Further, we included the preliminary analyses of a small sample of unaffected first-degree relatives, with the aim of prompting further research into familial vulnerability. We hypothesized that OCD patients and their unaffected siblings would show abnormal rich-club organization and rich-club connectivity in their white-matter network.

2. Materials and Methods

2.1. Participants

The study included 44 patients diagnosed with OCD who were medication-free for at least 4 weeks at the time of enrolment (mean age 38.5±9.9 year), 15 of their unaffected siblings (SIB, mean age 38.1±14.1) and 37 healthy controls (HC, mean age 39.5±11.5

year), matched on age, sex and education level. Details about the sample and recruitment have been described elsewhere (22). Briefly, patients were excluded in case of current psychoactive medication use, current or past psychosis, current or past alcohol usage disorder, major physical or neurological illness or in the presence of MRI contra-indications. Psychiatric comorbidity did not constitute a reason for exclusion, as long as the primary diagnosis was OCD, without predominant hoarding. Clinical characteristics were assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS, symptom list and severity scale) (23), the Obsessive-Compulsive Inventory-Revised (OCI-R) (24) and the Montgomery-Åsberg Depression Rating Scale (MADRS) (25). All participants were screened on axis I psychiatric disorders using the Structural Clinical Interview for DSM-IV-TR Axis I Disorders (26). Siblings should not meet lifetime criteria for OCD nor for any psychiatric diagnosis. Healthy controls had no current psychiatric diagnosis nor a family history of OCD.

2.2. MRI acquisition

MRI was performed using a 3-Tesla MR system (Signa HDxt, GE Healthcare, Milwaukee, USA) equipped with an eight-channel phased-array head coil. Diffusion-weighted echo-planar imaging (DWI) was collected at 30 randomly distributed diffusion weighted (b=1000 s/mm^2) and five reference (b=0 s/mm2) volumes with 49 axial slices at 2.4mm thickness covering the whole brain (repetition time TR=14000ms, echo time TE=85ms). The acquired in-plane resolution was 2.0x2.0mm, which was reconstructed to 1.0x1.0mm. Parallel imaging was applied with an acceleration factor of 2. Structural images were acquired using a 3D sagittal T1-weighted sequence (TR=7.8ms, TE=3ms, TI=450ms, FlipAngle=12, voxel size 1.0x.0.977x0.977mm, 172 slices).

2.3. Image preprocessing

Diffusion MRI data were preprocessed using the FMRIB Software Library (FSL version 6.0; http://www.fmrib.ox.ac.uk/fsl) and Advanced Normalization Tools (ANTs version 3.0; http://stnava.github.io/ANTs/). Images were corrected for motion and eddy current-induced susceptibility distortions by applying affine alignment of each diffusion-weighted image to the mean b=0 image (27). EPI-induced distortions correction was performed by nonlinear registration of the DWI to T1 (28), using ANTs' symmetric normalization *SyN* registration algorithm (29). We visually inspected the output of registration for all participants.

FSL's *bedpostX* (30) was used to estimate the voxel-wise diffusion parameter distributions. We ran *probtrackx2* for probabilistic fiber tracking with crossing fibers with the following parameters: 2000 steps per samples with a steplength of 0.5mm, curvature threshold of 0.2 and volume fraction set to 0.1, sampling a total of 5000

streamline fibers per voxel and keeping all other default parameters. We corrected path distribution for the length of the pathways.

Tracking was performed by seeding from 210 bilateral cortical regions and 36 bilateral subcortical regions obtained from the Brainnetome Atlas (31). Adding to this set, the subthalamic nucleus and the bed nucleus of the stria terminalis were obtained from the Subthalamic Nucleus Atlas (32) and from a probabilistic map of the National Institute of Mental Health (https://afni.nimh.nih.gov), respectively. All seeds (n=250) were registered from standard to native space following previously described methods (33). Briefly, T1 images were registered to the MNI1521mm brain template using ANTs' *SyN* registration tools (29). *antsApplyTransforms* was used to warp the cortical and subcortical seeds from MNI to native space by concatenating the inverse of warp fields and generic affine matrix using *GenericLabel[Linear]* as interpolation method. All masks were thresholded (at 50) and binarized.

2.4. Network construction

For each participant, a brain network was reconstructed with the cortical and subcortical seeds representing its *nodes*, and the white-matter tracts interconnecting them representing its *edges*. For each pair of nodes, the value of each edge was assigned as the number of reconstructed streamlines (NOS). First, the arithmetic average of NOS connecting node (i,j) and that connecting (j,i) was obtained to create an undirected network. Next, proportional thresholding of the network edges was applied by retaining only a proportion (.23) of the strongest network edges (34). Further, only those edges that were present in at least 60% of all group members were retained, calculated per group separately (35). Next to NOS-weighted networks, binary networks were computed (i.e., thresholded edge weights were set to 1, 0 otherwise). The stability of the results was checked using proportional thresholds of .30 and .55 (Supplementary Material).

2.5. Network characteristics

All graph measures were computed using the Brain Connectivity Toolbox (36) in Matlab (Matlab R2019b; Mathworks Inc). Basic network characteristics such as network density (i.e., fraction of present connections to possible connections, ignoring edge weights) and overall network connectivity (i.e., sum of edge weights across all nodes) were compared between groups for the raw and thresholded networks. Following the two-step thresholding procedure, obtained networks were checked to preserve key properties of biological networks, namely connectedness (i.e., > 80% of nodes being connected to at least another node) and small-world topology (i.e., a small-world index > 1) (37). Global and local graph measures of efficiency and clustering coefficient were computed on the weighted networks (Supplementary Material).

2.6. Rich-club analysis

A schematic representation of the rich-club analysis steps is shown in **Figure 1**.

Rich-club organization. Computing the rich-club coefficient Ø at degree level of *k* allows characterizing the rich-club behavior of a network (6). In the topological, unweighted rich-club (Ø), rich-club nodes preferentially create connections between each other. In the weighted rich-club ($Ø^w$), rich-club nodes preferentially allocate the strongest weights to the connections between them (38). The empirical Ø and $Ø^w$ were computed on the binary and NOS-weighted networks respectively, and normalized by the averaged rich-club curve of a set of comparable random networks ($Ø_{rand}$) (6). For each network, a population of 1,000 random networks was generated by rewiring the edges of the original matrix, while preserving its connection density, degree and strength distribution (39). A normalized coefficient $Ø_{norm} > 1$ (calculated as $Ø/Ø_{rand}$) is indicative of rich-club organization in a network (40) and is assigned a (one-sided) p-value by calculating the proportion of $Ø_{rand}$ that exceeded the empirically measured metric Ø (FDR-corrected at q=0.05).

Nodes classes: rich-club vs non-rich club. Rich-club nodes (i.e., nodes with degree > *k*) were defined for each participant as the top 16% ($k > 38$) highest-degree regions (6). The regions classified as rich-club nodes common to all participants were then selected as the final set and used for subsequent analyses, as previously reported (6). This was done separately for the two-group (OCD vs. HC, n=56) and the three-group (n=64) comparisons. Analyses were repeated considering smaller and larger sets of hub regions (including from the top 5% to the top 25% highest degree-regions) (Supplementary Material).

Connections classes: rich-club, feeder and local. Structural connections between nodes were classified accordingly into rich club (i.e., between rich-club nodes), feeder (i.e., between rich-club and non-rich-club nodes) and local (i.e., between non-rich-club nodes) connections. Two measures of connectivity were calculated for each connection class and compared between groups. Connectivity *strength* was defined as the sum of all edge weights (i.e., sum of all NOS) within each connection class. Weighted connectivity *density* was defined as the ratio of the connectivity strength of each connection class to the connectivity strength of the whole brain, representing an index of network topology (5).

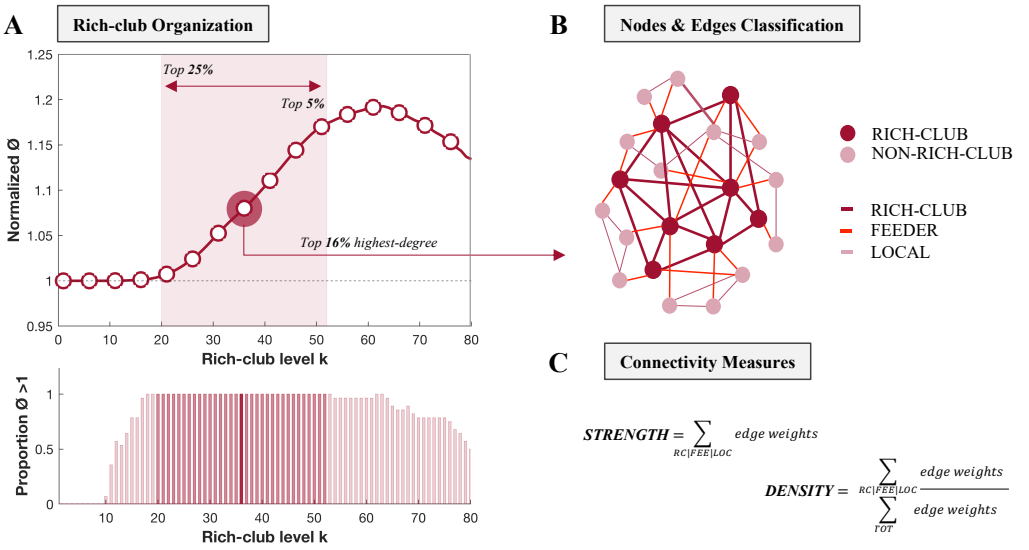

Figure 1. Schematic representation of the rich-club analysis. First, rich-club coefficients Ø (unweighted and weighted) are calculated at increasing rich-club levels *k* and normalized by the averaged rich-club curve of a set of comparable random networks. A schematic representation of the normalized groups average rich-club curve is shown (*A top*). Normalized Ø > 1 (dashed line in *A top*) indicates significant rich-club organization in a network. The bar graph represents the proportion p of participants for which this holds true across rich-club levels (p=1 indicates that all participants display significant rich-club organization) (*A bottom*). Next, the nodes of the network are classified into rich-club or non-rich-club nodes (*B*). Members of the rich-club are defined as the most highly connected nodes of the network common to all participants. Main results are reported for the top 16% highest-degree regions, but a wider range is considered, including from the top 25% to the top 5% highest-degree regions (red shaded area in *A top and bottom*). Network edges are classified accordingly into rich-club (connections between rich-club nodes), feeder (connections between rich-club and non-rich-club nodes) and local (connections between non-rich-club nodes) (*B*). Two connectivity measures are finally computed; connectivity strength represents the sum of all edge weights within each connection class, and weighted connectivity density represents the ratio of the connectivity strength of each connection class to the connectivity strength of the whole brain (*C*). RC: rich-club connections; FEE: feeder connections; LOC: local connections; TOT: whole-brain connections.

2.7. Statistical analysis

ANOVA was used to compare age, years of education, sex and clinical variables between groups. Comparisons of network characteristics were performed using non-parametric permutation testing for randomizing group assignment (separately for OCD-HC, OCD-SIB, SIB-HC) (41). 50,000 permutations of group assignments yielded an empirical null distribution of effects under the hypothesis of no difference between groups. The measured difference was assigned a (two-sided) p-value, as the percentage of the computed null distribution greater than or equal to the empirically measured metric. The same procedure was followed to compare rich-club measures between OCD patients and controls. We separately tested for ordered differences between the three

groups using the Jonckheere-Terpstra test (Supplementary Material). Group comparisons of rich-club coefficients were iterated over the range of increasing *k* displaying significant rich-club organization ($Ø_{norm}$>1) for at least 97% of participants, and a false-discovery rate (FDR) threshold of q=.05 was applied on the obtained p-values. Spearman's partial correlation coefficients were calculated in the OCD group to investigate the relationship between rich-club measures and clinical variables (Y-BOCS and OCI-R total and sub-scores, disease duration and MADRS), while controlling for age, sex and education. The area under the curve (AUC) was computed for rich-club, feeder and local measures across the range of increasing *k* considered for the between-group comparisons.

Table 1. Demographic and clinical characteristics of OCD patients, their unaffected siblings and healthy controls.

	OCD patients (n = 28)	**Siblings** (n = 8)	**HC** (n = 28)	**Analysis**
	Mean (**± SD)**	***Mean (*** **± SD)**	***Mean (*** **± SD)**	***F (p-value)***
Demographic variables				
Age[1]	36.8 (±9.2)	37.8 (±13.2)	40.6 (±11.0)	0.99 (.378)
Education[1]	13.6 (±3.4)	12.3 (±2.4)	12.2 (±2.8)	1.55 (.219)
Sex (M/F)	11/17	4/4	12/18	0.14 (.866)
Clinical variables				
Disease duration[1]	22.7 (±11.3)	0	0	66.5 (< .001)
Y-BOCS (total score)	21.3 (±6.0)	0.1 (±0.4)	0	220 (< .001)
Y-BOCS Obsessions	10.3 (±3.6)	0.1 (±0.4)	0	146 (< .001)
Y-BOCS Compulsions	11.0 (±3.0)	0	0	236 (< .001)
OCI-R (total score)	22.8 (±11.7)	2.9 (±2.9)	3.3 (±5.4)	37.3 (< .001)
OCI-R Washing	3.0 (±3.6)	0	0.4 (±0.7)	7.97 (< .001)
OCI-R Checking	6.4 (±4.2)	0.6 (±0.9)	0.3 (±0.6)	32.5 (< .001)
OCI-R Ordering	4.4 (±3.7)	0.4 (±0.7)	0.9 (±1.8)	12.4 (< .001)
OCI-R Obsession	4.9 (±3.5)	0.6 (±1.2)	0.4 (±1.6)	21.1 (< .001)
OCI-R Hoarding	1.8 (±2.6)	1.1 (±1.4)	1.2 (±2.2)	0.4 (0.67)
OCI-R Neutralizing	2.1 (±3.0)	0.1 (±0.4)	0.1 (±0.2)	7.46 (< .001)
MADRS	9.3 (±6.9)	1.3 (±2.9)	1.0 (±1.6)	20.6 (< .001)

1 expressed in years; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; OCI-R = Obsessive-Compulsive Inventory Revised; MADRS = Montgomery-Åsberg Depression Rating Scale; SD = Standard Deviation of the mean; HC = Healthy Controls

3. Results

3.1. Demographic and clinical characteristics

Following visual inspection of the raw images, 16 OCD patients, 7 unaffected siblings and 9 healthy controls were excluded from subsequent analyses, due to positioning of

the field of view resulting in (major) cuts of the bilateral temporal pole. The final sample thus included a total of 28 OCD patients (mean age 36.8±9.2 year), 8 unaffected siblings (mean age 37.8±13.2 year) and 28 healthy controls (mean age 40.6±11.0 year). Age, sex and education did not differ significantly between the three groups (**Table 1**). OCD patients displayed significantly higher Y-BOCS, OCI-R and MADRS scores compared to their unaffected siblings and controls (**Table 1**).

3.2. Network characteristics

No significant differences in network density (p=.26) and overall network connectivity (p=.53) emerged, both looking at the raw and thresholded networks of OCD patients and healthy controls (**Table S1**). Compared to the latter, OCD patients displayed significantly higher global clustering coefficient (p=.03), but no differences in global efficiency (p=.64) or small world-topology (p=.82) (**Table S1**). OCD patients also displayed significantly higher local efficiency for n=7 nodes and higher local clustering for n=74 nodes ($q < .05$), spanning extensive frontal and temporal areas, cingulate cortex, lateral occipital cortex and subdivisions of the thalamus, among others (**Table S2**). Unaffected siblings presented with significantly lower overall network connectivity ($p < .001$), lower global efficiency ($p < .001$) and lower global clustering coefficient ($p < .001$) compared to OCD patients and healthy controls. On the other hand, following the two-step network thresholding procedure, siblings displayed significantly higher network density ($p < .001$). The details and implications of these results are outlined in the Supplementary Material.

3.3. Rich-club organization

Rich-club organization was found in the white-matter networks of both OCD patients and healthy controls ($Ø_{norm}$ range k=20 to k=53; $Ø_{norm}^{w}$ range k=42 to k=63) (**Figure 2** *A, C*). Compared to controls, OCD patients displayed significantly lower topological rich-club organization (range k=29 to k=40, $q < .01$, Hedge's $g = [.81,1.48]$). OCD patients also displayed lower weighted rich-club organization for the range k=42 to k=56, although this difference was not significant ($q > .34$). A significantly lower weighted $Ø_{norm}^{w}$ was found when using proportional thresholds of .30 and .55 (**Figure S1**).

The three-group analysis revealed significant ordered differences between groups for both topological (HC > OCD > SIB, range k=20 to k=53, $q < .05$) and weighted (SIB > HC > OCD, k=42 to k=58, $q < .05$) rich-club organization (Supplementary Material, **Figure S3**).

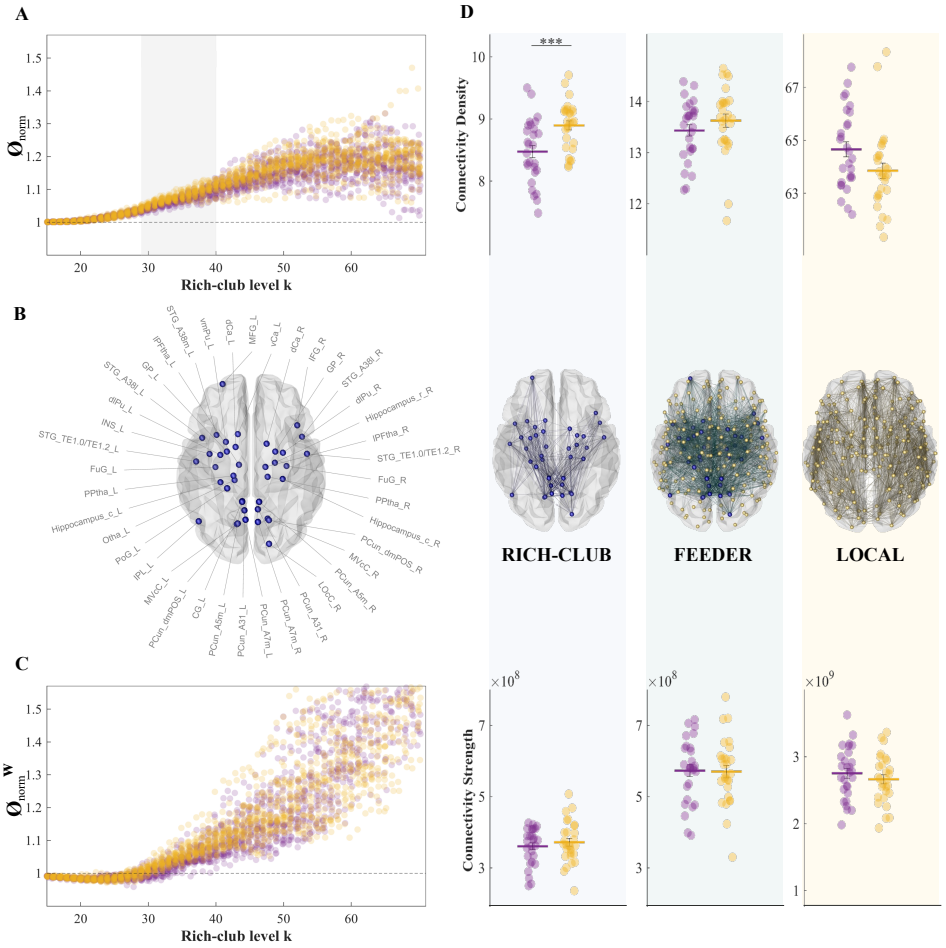

Figure 2. Individual normalized Ø and Ø^{w} are plotted for OCD patients (purple) and healthy controls (yellow) for different rich-club levels. Normalized Ø > 1 (dashed line in *A* and *C*) indicates significant rich-club organization. The grey shaded area indicates where rich-club organization of the two groups is significantly different ($p < 0.01$, FDR-corrected) (*A, C*). Rich-club nodes are selected as the top 16% highest-degree nodes of the network (*B*), and network edges are classified accordingly into rich-club, feeder and local (*D* middle). Topological (i.e., connectivity density; *D* top) and weighted (i.e., connectivity strength; *D* bottom) properties are calculated for each connection class and compared between groups. ***: $p < .001$ MFG: middle frontal gyrus; IFG: inferior frontal gyrus; STG: superior temporal gyrus; FuG: fusiform gyrus; IPL: inferior parietal lobule; Pcun: precuneus; PoG: postcentral gyrus; INS: insular gyrus; CG: cingulate gyrus; MVcC: medioventral occipital cortex; LocC: lateral occipital cortex; vCA: ventral caudate; GP: globus pallidus; vmPu: ventromedial putamen; dCa: dorsal caudate; dlPu: dorsolateral putamen; Pptha: posterior parietal thalamus; Otha: occipital thalamus; lPFtha: lateral pre-frontal thalamus; L: left; R: right; OCD: obsessive-compulsive disorder patients; HC: healthy controls.

3.4. Connectivity strength and density of rich-club, feeder and local connections

Consistent with previous reports, rich-club nodes selected at the top 16% highest-degree nodes across OCD patients and controls included the middle and inferior frontal gyrus, superior temporal gyrus, fusiform gyrus, inferior parietal lobule, precuneus, postcentral gyrus, insula, cingulate gyrus, ventral and lateral occipital cortex and, subcortically, the hippocampus, (posterior parietal, occipital and lateral pre-frontal) thalamus and regions of the basal ganglia (caudate, putamen, globus pallidus) (6, 20, 21) (**Figure 2** *B*).

No significant differences between groups were found in the connectivity *strength* of either rich-club (p=.45), feeder (p=.91) or local (p=.37) connections (**Figure 2** *D* bottom). OCD patients displayed significantly lower rich-club weighted connectivity *density* (p < .001, Hedge's g =.94) and a trend to increased local connectivity density (p=.052, Hedge's g =.53) compared to controls. No significant differences were observed for feeder connectivity density (**Figure 2** *D* top). Results were stable when using proportional thresholds of .30 and .55 (**Figure S2**).

Unaffected siblings displayed the highest rich-club and local connectivity density, but the lowest feeder connectivity density (Supplementary Material, **Figure S3**).

3.5. Correlations with clinical characteristics

The AUC computed for rich-club organization [*Mean (±SD):* $Ø_{norm}$=35.71 (±0.37), $Ø_{norm}^{w}$=26.05 (±3.25)], and for strength and weighted density of rich-club [strength=4.65e+09 (±6.84e+08), density=109.13 (±6.98)], feeder [strength=9.05e+09 (±1.37e+09), density=212.23 (±9.16)] and local [strength=5.82e+10 (±8.2e+09), density=1.37e+03 (±23.67)] connections was correlated with clinical characteristics (Y-BOCS and OCI-R total and sub-scores, disease duration and MADRS, **Table 1**), while controlling for age, sex and education. No significant correlations are reported (**Table S3**).

4. Discussion

The current study used probabilistic tractography to investigate white-matter rich-club organization in OCD. Compared to healthy controls, OCD patients displayed significantly lower unweighted and, to some extent, weighted rich-club organization, suggesting that brain network hubs exhibit less connections between them, and do not necessarily allocate the strongest weights thereto (38). OCD patients congruously displayed significantly lower rich-club weighted connectivity *density*, representing a smaller fraction of all connection weights allocated to the rich-club compared to the healthy counterpart. On the other hand, no differences emerged between groups when comparing connectivity *strength* in absolute terms, neither for whole-brain, rich-club,

feeder nor local connections. Thus, our results mostly point to differences in the topological arrangement of connections and their weights to the rich-club, rather than absolute differences in the strength of such connections. While still being able to draw on comparable resources, OCD patients might manage their connectivity system differently, allocating more weight to peripheral connections at the detriment of a central core of hub nodes. Consistent with this hypothesis, OCD patients also displayed a trend to increased local weighted connectivity density, meaning that a higher fraction of all connection weights is allocated to local connections compared to healthy controls.

Rich-club organization is regarded as a marker of network integration, allowing distant regions to quickly and effectively exchange information between each other (7). Efficient brain networks however stem from the delicate balance between integration and segregation of functions, thus equally relying on the specialization of regions, or clusters of regions, to take on specific tasks (36). In patients with OCD, the scale might be tipped in favor of a more segregated network. As opposed to lower rich-club organization, we found OCD patients to display significantly higher global clustering coefficient, local efficiency and local clustering specifically of non-rich-club nodes. These results are consistent with previous evidence of decreased rich-club connectivity (21) and decreased global efficiency as opposed to increased clustering (18, 21), while disagreeing with the pattern described by Zhou et al. Zhou, Ping (20), pointing to higher measures of network efficiency in OCD. After all, the susceptibility of graph measures to specific methodological choices cannot be neglected. The methods used by the present and previous studies differed considerably on multiple fronts. As opposed to deterministic tractography, we employed probabilistic tractography to map the connectomes of OCD patients. Furthermore, we used a brain parcellation with a higher resolution compared to what previously used, a methodological difference of the known potential impact on connectivity measures (42, 43). Nonetheless, despite the technical differences, results across studies point to altered efficiency of information transfer across the brain, yet awaiting for further research to clarify the nature of rich-club organization anomalies in OCD.

For both OCD patients and healthy controls, rich-club nodes included areas of frontal, parietal, temporal and occipital cortices, next to subdivisions of the insula and cingulate cortex, and subcortical regions of the basal ganglia, thalamus and hippocampus, to a large extent consistent with what previously reported (7, 20, 21). The literature linking dysfunctional nodes of the cortico-striatal-thalamo-cortical loops to OC symptomatology is extensive and includes several lines of evidence, ranging from early positron-emission tomography studies demonstrating metabolic abnormalities to volumetric, functional and lesion studies, all pointing to the critical involvement of the frontal as well as subcortical components of these circuits (44). Beyond this traditional

view, a potentially central role has been ascribed to the dorsal anterior cingulate cortex (dACC), hub in the cognitive control and fear learning and extinction networks, exerting control signals via extensive connections with surrounding cortical and subcortical structures to direct behavioral responses (45). Not only central to a mechanistic theory on the emergence of obsessions and compulsions, the dACC is also the target of surgical and neuromodulatory treatment interventions (45, 46), placing it under the spotlight of OCD brain dynamics. Additionally, many of the identified rich-club nodes critically participate in RSNs like the default mode, salience and frontoparietal networks, the inter- and intra-connectivity of which has consistently been reported altered in OCD (47). However, despite the overlap between rich-club nodes and the regions generally implicated in OCD pathophysiology, the question arises about the specificity of rich-club organization anomalies to OCD. No significant correlation between any rich-club measure and OCD-specific clinical characteristics were found in neither the present nor some of the previous studies (19, 21). A recent meta-analysis comprising almost 900 patients across 12 neurological and psychiatric disorders found that rich-club connections were disproportionally affected across disorders compared to peripheral connections (48), and independent studies reporting altered rich-club organization in single disorders are numerous (13-17). It has been suggested that, because of their central embedding in the network, central regions and connections might be not only particularly vulnerable to various disease processes themselves (49), but also at increased risk of propagating these processes across the network (50, 51). Given the importance of central connections for appropriate cognitive function (6, 52), any defect that might affect this system could then result in various forms of cognitive impairment. Considering that deficits in cognitive function overlap across disorders (53), it is possible that abnormal rich-club organization constitutes a transdiagnostic vulnerability marker to psychopathology in general, mediating dysfunctional traits common across diagnostic categories rather than specific symptoms. Future studies should further address this hypothesis, trying to identify unique and/or common cognitive markers relating to rich-club dysfunction in OCD with respect to other brain disorders.

Alternatively, the absence of disease severity effects could point to rich-club organization anomalies being trait rather than state markers of OCD. Family-based studies are valuable tools to unravel putative vulnerability markers of a disorder, indexing a genetic liability and allowing the dissection of state and trait signatures. The present study preliminarily investigated rich-club organization in a small group of unaffected siblings. Generally, neuroimaging markers of anomaly present in both patients and unaffected first-degree relatives, but not in healthy controls, are good candidates, and potential endophenotypes have been identified in measures of white-matter microstructure (22, 54, 55), network properties (56) and functional patterns of

dysconnectivity (57-59). Research on whether rich-club organization could be considered as such is limited, with only one study reporting intermediate levels of rich-club connectivity in unaffected siblings (21). Our results however revealed a pattern of higher weighted rich-club organization and rich-club density in unaffected siblings compared to OCD patients and healthy controls, as opposed to lower unweighted rich-club organization. Although limited in their generalizability by the small sample size, our results point to a buffering mechanism that unaffected first-degree relatives may put in place. Namely, they might recruit additional resources (in terms of a higher fraction of all connection weights) to preserve cognitive performance and mental health in spite of a reduction in the number of rich-club connections (i.e., unweighted rich-club organization). Although no previous research investigated changes in the trade-off between topological and weighted rich-club measures, the idea of a buffering mechanism is congruous with e.g., reports of increased resting-state connectivity between cognitive control networks in unaffected siblings (60). However, longitudinal and developmental studies are needed to correctly place rich-club organization along the trajectory to OCD manifestation or, if considered as transdiagnostic marker, psychopathology in general.

The current study has some limitations. First, due to fitting of the field of view during MRI acquisition resulting in major cuts of the temporal pole, many participants were excluded from the current analyses, reducing the available sample size. Despite the strong effect sizes reported, future studies should aim to include larger samples. Specially, findings concerning the group of unaffected siblings are to be taken with extreme caution, and are mostly intended to suggest hypotheses that could be addressed by future studies. Additionally, inherent limitations of the DWI sequence and probabilistic tractography urge us to interpret the results carefully. More advanced protocols such as multi-shell procedures will allow the implementation of processing and tractography methods offering better control over the biological plausibility of the reconstructed white-matter pathways (61).

5. Conclusions

We investigated rich-club organization in a sample of unmedicated OCD patients. Our results suggest a topological shift of connections and their weights away from the rich-club, resulting in weaker structural connectivity between network hubs. Preliminary findings of increased rich-club organization in unaffected siblings hint at a neuroimaging feature worth investigating further in the context of familial vulnerability or resilience to developing the disorder. We finally underscore the importance of looking at network-based alterations in brain organization and function when investigating OCD.

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Supplementary Material

1. Network characteristics

Network density (i.e., fraction of present connections to possible connections, ignoring edge weights) and overall network connectivity (i.e., sum of edge weights across all nodes) were first computed for the raw networks (i.e., before any thresholding procedure was applied). Permutation testing (50,000 permutations) revealed no significant differences between OCD patients and healthy controls in neither of these measures (see **Table S1**). Following the two-step thresholding procedure, the networks of both groups of subjects showed to preserve connectedness (> 80% of nodes connected to at least one other node) and small-world topology (small-world index > 1). Again, no significant differences between groups were detected for neither network density, overall network connectivity or small-worldness (see **Table S1**).

Global efficiency (i.e., the average of inverse shortest path length) and global clustering coefficient (i.e., average clustering coefficient across all nodes of the network) were additionally computed on the thresholded weighted networks, employing the *"efficiency_wei.m"* and *"clustering_coef_wu.m"* functions from the Brain Connectivity Toolbox, respectively. No differences were detected between the global efficiency of OCD patients and healthy controls, whereas OCD patients displayed significantly increased global clustering coefficient (p=.03, see **Table S1**).

Local efficiency and local clustering coefficients were calculated for each node of the weighted network (n=250). P-values obtained with permutation testing were corrected for multiple comparisons (FDR at $q < .05$). OCD patients displayed significantly increased local efficiency in the left orbital and postcentral gyrus, and in the right superior temporal gyrus, superior parietal lobule and lateral occipital cortex. The right middle and inferior temporal gyrus, and the right posterior superior temporal sulcus displayed significantly reduced local efficiency in OCD patients (see **Table S2**). Notably, all these nodes belonged to the pool of non-rich-club nodes. A total of n=74 nodes displayed significantly increased clustering coefficient in OCD patients compared to healthy controls, and are listed in **Table S2**. The majority of these nodes (n=58) again belonged to non-rich-club nodes. The right middle and inferior temporal gyrus, and the right posterior superior temporal sulcus displayed significantly decreased clustering coefficient in OCD patients (see **Table S2**).

2. Validation analyses: smaller and larger sets of rich-club nodes

For the two-group comparison (OCD vs. HC), rich-club nodes were selected as the nodes with a degree $k > 38$, including the top 16% highest-degree nodes of the network common to all patients and controls (n=56). However, smaller and larger sets of rich-club nodes were also considered, including nodes with a degree $k > 32$ (top 25%) to $k > 51$ (top 5%). Rich-club, feeder and local connectivity *strength* and weighted *density* were calculated across this range, and are displayed in **Figure S2**.

Results were consistent across k levels; no significant differences emerged for neither rich-club, feeder nor local connectivity *strength*. OCD patients displayed significantly reduced rich-club weighted connectivity *density* for the range $k > 32$ (top 25%) to $k > 42$ (top 11%) ($p < .05$, Hedge's $g = [0.64, 0.94]$). Nevertheless, the observed difference between all measures followed a similar trend across rich-club sets, regardless of statistical significance.

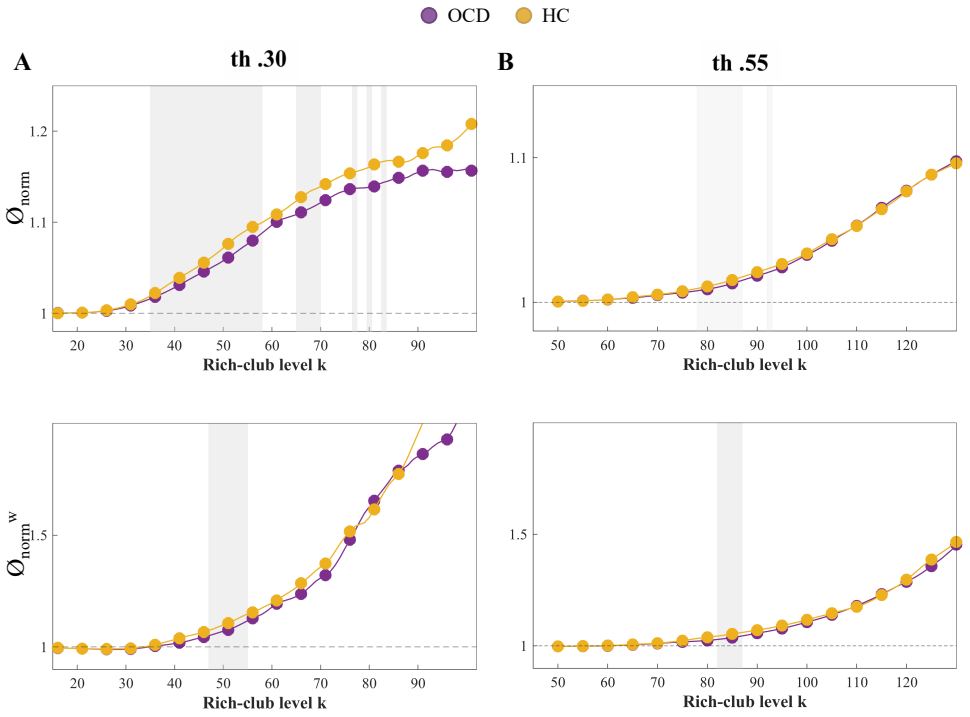

Figure S1. The group average normalized Ø (*A, B* top) and Ø^{w} (*A, B* bottom) are plotted for OCD patients (purple) and healthy controls (yellow) for the proportional thresholding parameters of .30 (*A*) and .55 (*B*). Normalized Ø > 1 (dashed line) indicates significant rich-club organization. The grey shaded area indicates where rich-club organization of the two groups is significantly different ($q < 0.05$). The lighter grey shaded area in panel *B* (top) indicates uncorrected p-values ($p < 0.05$). OCD: obsessive-compulsive disorder patients; HC: healthy controls; th: proportional threshold.

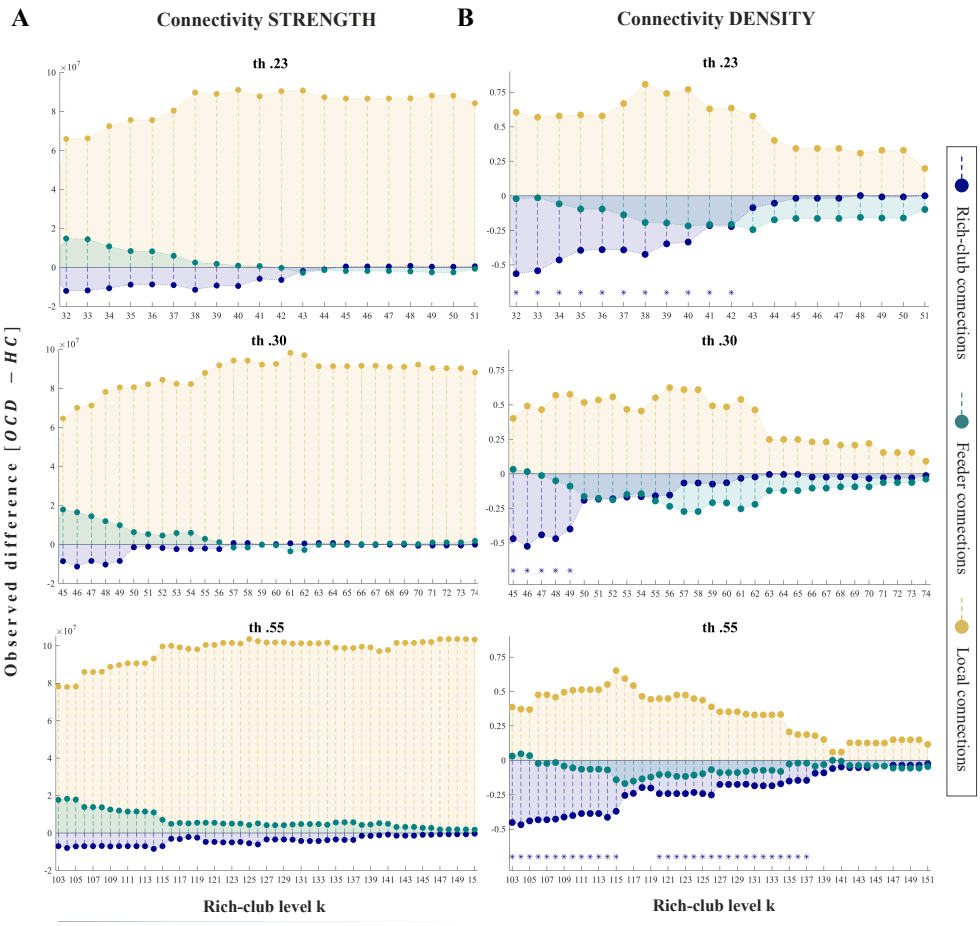

Figure S2. The difference between the rich-club, feeder and local connectivity strength (*A*) and density (*B*) of OCD patients and healthy controls is plotted for the networks constructed using a proportional threshold of .23 (*A, B* top), .30 (*A, B* middle) and .55 (*A, B* bottom). The connectivity measures are calculated over a range of rich-club levels *k* that always include from the top 5% to the top 25% highest-degree nodes of the network. Between-group differences are observed across proportional thresholding parameters for a range of *k* levels for rich-club connectivity density (blue asterisks in *B*). *: $p < 0.05$; OCD: obsessive-compulsive disorder patients; HC: healthy controls; th: proportional threshold.

3. Validation analyses: proportional thresholding parameters

The stability of the results was checked using proportional thresholds of .30 and .55 to construct NOS-weighted and binary networks.

Threshold .30. Rich-club organization was found in the white-matter network of both OCD patients and healthy controls ($Ø_{norm}$, range k=27 to k=87; $Ø_{norm}^{w}$, range

k=47 to *k*=140). OCD patients displayed significantly reduced topological rich-club organization (range *k*=35 to *k*=58, q < .05, Hedge's g = [0.72,1.71]; range *k*=65 to *k*=70; q < .05; Hedge's g = [0.61,0.94]; *k*=75, q=.049; Hedge's g = [0.59]; *k*=77, q=.04; Hedge's g = [0.63]; *k*=80, q=.02; Hedge's g = [0.74]; *k*=83, q=.04; Hedge's g = [0.64]). OCD patients also displayed significantly reduced weighted rich-club organization (range *k*=47 to *k*=55, q < .05, Hedge's g = [0.54,0.79]) (**Figure S1**).

Rich-club nodes selected at the top 16% (*k* > 53) highest-degree nodes at the group level included the same brain regions reported in the main text. Rich-club, feeder and local connectivity strength and connectivity density were computed across a range of rich-club levels (from *k*=45 to *k*=74), including the top 25% to the top 5% highest-degree nodes of the network. No significant differences between groups were found across this range for neither rich-club, feeder nor local connectivity *strength*. OCD patients displayed significantly reduced rich-club weighted connectivity *density* when rich-club nodes were selected at the top 25% to the top 20% highest-degree nodes (p < .01, Hedge's g = [0.74,0.85]) (**Figure S2**).

Threshold .55. Rich-club organization was found in the white-matter network of both OCD patients and healthy controls ($Ø_{norm}$, range *k*=54 to *k*=201; $Ø_{norm}^{w}$, range *k*=82 to *k*=194). OCD patients displayed significantly reduced topological rich-club organization (range *k* =78 to *k* =87, range *k* =92 to *k* =93, p < .05, uncorrected; Hedge's g = [0.55,0.69]), as well as significantly reduced weighted rich-club organization (range *k* =82 to *k* =87, q < .01, Hedge's g = [0.48,1.04]) (**Figure S1**).

Rich-club nodes selected at the top 16% (*k* > 118) highest-degree nodes at the group level included the same brain regions reported in the main text. Rich-club, feeder and local connectivity strength and connectivity density were computed across a range of rich-club levels (from *k* =103 to *k* =151), including the top 25% to the top 5% highest-degree nodes of the network. No significant differences between groups were found across this range for neither rich-club, feeder nor local connectivity *strength*. OCD patients displayed significantly reduced rich-club weighted connectivity *density* when rich-club nodes were selected at the top 25% to the top 10% highest-degree nodes (p < .05, Hedge's g = [0.60,0.78]) (**Figure S2**).

4. Group comparisons including the unaffected siblings

A final sample of 8 unaffected siblings (mean age 37.8±13.2 year) was included (see **Table 1** for demographic and clinical characteristics). Analysis of rich-club organization was carried out as described in the main text. However, in light of baseline differences in network density and connectivity, only rich-club, feeder and local weighted connectivity *density* were considered (see below). Group comparisons of the observed

effects were performed using the Jonckheere-Terpstra test, a nonparametric test for ordered differences in three or more study populations. The permutation version of the test (50,000 permutations) was used for the reference null distribution and the resulting one-sided p-value. Specific hypotheses on the direction of the ordered differences were formulated based on inspection of the data. Analyses were performed in R (https://CRAN.R-project.org/package=clinfun).

Network characteristics. The white-matter network of the unaffected siblings presented with significantly lower overall network connectivity and significantly lower network density compared to OCD patients and healthy controls ($p < .001$, **Table S1**). These group differences were retained for overall network connectivity following the two-step thresholding procedure. However, the direction of the differences reversed for the density of thresholded networks, with the unaffected siblings displaying significantly higher network density compared to OCD and healthy controls ($p < .001$, **Table S1)**. To avoid introducing any bias, only graph measures including some form of normalization (either by a null distribution or by the overall network connectivity) were considered for the comparisons including the siblings group. Following the two-step thresholding procedure, the networks of all subjects showed to preserve connectedness (> 80% of nodes connected to at least one other node) and small-world topology (small-world index > 1). The unaffected siblings displayed significantly higher small-world properties, but significantly lower global efficiency and global clustering coefficient compared to OCD patients and healthy controls ($p < .001$, **Table S1**). Differences in local efficiency and local clustering between the unaffected siblings and OCD patients and healthy controls spanned almost the entire network (n=229 and n=217 nodes respectively, $q < .05$).

Rich-club organization. For all three groups of subjects, significant rich-club organization was observed over a range of rich-club levels ($Ø_{norm}$, range k =20 to k =53; $Ø_{norm}{}^{w}$, range k =42 to k =67). The Jonckheere-Terpstra test revealed significant ordered differences between groups, with HC > OCD > SIB topological rich-club organization (range k =20 to k =53, JT = [120, 450], $q < .05$) and SIB > HC > OCD weighted rich-club organization (range k =42 to k =58, JT = [310, 588], $q < .05$) (**Figure S3**).

Rich-club, feeder and local connectivity. Rich-club nodes selected at the top 16% highest-degree nodes across all groups of subjects ($k > 35$, n=64) included the same areas reported in the main text. We found significant ordered differences between groups for rich-club, feeder and local connectivity density. However, the direction of the ordered differences was different across connection classes, with SIB > HC > OCD rich-club connectivity density (JT = 329, $p < .001$); HC > OCD > SIB feeder connectivity density (JT = 384, $p < .001$) and SIB > OCD > HC local connectivity density (JT = 419, $p = .01$) (**Figure S3).** This pattern of results was stable across larger and smaller sets of

rich-club nodes (range from $k > 29$ to $k > 51$, including from the top 25% to the top 5% highest-degree nodes).

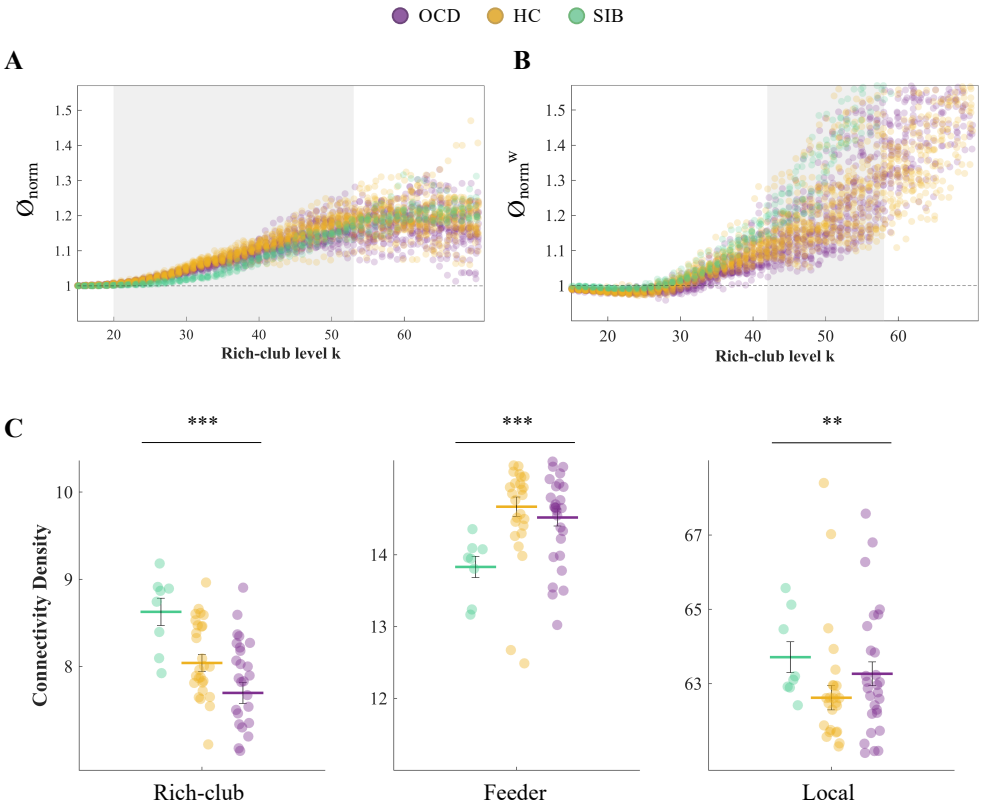

Figure S3. Individual normalized Ø and Ø^{w} are plotted for OCD patients (purple), healthy controls (yellow) and unaffected siblings (green) for different rich-club levels. Normalized Ø > 1 (dashed line in *A* and *B*) indicates significant rich-club organization. The grey shaded area indicates significant ordered differences between groups (HC > OCD > SIB, q < 0.01, *A*) (SIB > HC > OCD, q < 0.05, *B*). Rich-club nodes are selected at the top 16% highest-degree nodes of the network ($k > 35$), and network edges are classified accordingly into rich-club, feeder and local (not shown). Rich-club, feeder and local connectivity density are tested for ordered differences between groups (*C*). ***: p < 0.001; **: p < 0.01; OCD: obsessive-compulsive disorder patients; HC: healthy controls; SIB: unaffected siblings.

Table S1. Basic network characteristics and global graph measures of OCD patients, their unaffected siblings and healthy controls.

	OCD patients (n = 28)	**Siblings (n = 8)**	**HC (n = 28)**
	Mean (± SD)	***Mean (± SD)***	***Mean (± SD)***
Pre-thresholding			
Network connectivity[1]	4.5e+09 (±6.7e+08)	3.2e+09 (±3e+08)	4.4e+09 (±6.6e+08)
	diff = 1.3e+09, p < .001		
		diff = -1.2e+09, p < .001	
	diff = 1.1e+08, p = 0.53		
Network density[2]	0.99 (±0.01)	0.68 (±0.05)	0.98 (±0.01)
	diff = 0.31, p < .001		
		diff = -0.31, p < .001	
	diff = 0.004, p = 0.26		
Post-thresholding			
Network connectivity[1]	4.3e+09 (±6e+08)	3.2e+09 (±3e+08)	4.2e+09 (±5.9e+08)
	diff = 1.1e+09, p < .001		
		diff = 9.9e+08, p < .001	
	diff = 8.3e+07, p = 0.60		
Network density[2]	0.15 (±0.005)	0.18 (±0.004)	0.15 (±0.006)
	diff = -0.03, p < .001		
		diff = 0.03, p < .001	
	diff = -1.9e-04, p = 0.91		
Network connectdeness[3]	100%	100%	100%
Small-worldness	3.65 (±0.54)	10.22 (±3.86)	3.59 (±0.98)
	diff = -6.58, p < .001		
		diff = 6.64, p < .001	
	diff = 0.05, p = 0.82		
Global efficiency	4.7e+05 (±6e+04)	3.9e+05 (±3e+04)	4.6e+05 (±5e+04)
	diff = 8.4e+04, p < .001		
		diff = -7.7e+04, p < .001	
	diff = 7.5e+03, p = 0.64,		
Global clustering	0.012 (±0.002)	0.006 (±5e-04)	0.011 (±0.002)
coefficient	*diff = 0.006, p < .001*		
		diff = -0.005, p < .001	
	diff = 0.001, p = .03		

[1]sum of edge weights across all nodes; [2]fraction of present connections to all possible connections, [3]percentage of nodes connected to at least one other node. Group comparisons are performed using permutation testing (50,000 permutations of group assignments). The observed difference is calculated in turn as OCD-SIB, SIB-HC, OCD-HC and is assigned a p-value. Diff: observed difference; SD: standard deviation; OCD: obsessive-compulsive disorder patients; SIB: unaffected siblings; HC: healthy controls.

Table S2. Local efficiency and local clustering coefficient differences between OCD patients and healthy controls.

	Local efficiency	**Local clustering**
ID Brainnetome atlas[1]	***p-value FDR-corrected (comparison)***	
Non-rich-club nodes		
2 – R Superior frontal gyrus (A8m)		** OCD > HC
3 – L Superior frontal gyrus (A8dl)		** OCD > HC
5 – L Superior frontal gyrus (A9l)		* OCD > HC
6 – R Superior frontal gyrus (A9l)		* OCD > HC
7 – R Superior frontal gyrus (A6dl)		* OCD > HC
12 – R Superior frontal gyrus (A9m)		* OCD > HC
19 – L Middle frontal gyrus (A46)		* OCD > HC
25 – L Middle frontal gyrus (A6vl)		* OCD > HC
31 – L Inferior frontal gyrus (IFS)		* OCD > HC
34 – R Inferior frontal gyrus (A45c)		* OCD > HC
36 – R Inferior frontal gyrus (A45r)		* OCD > HC
40 – R Inferior frontal gyrus (A44v)		* OCD > HC
43 – L Orbital gyrus (A12/47o)	** OCD > HC	*** OCD > HC
44 – R Orbital gyrus (A12/47o)		** OCD > HC
45 – L Orbital gyrus (A11l)		* OCD > HC
47 – L Orbital gyrus (A11m)	** OCD > HC	*** OCD > HC
48 – R Orbital gyrus (A11m)		* OCD > HC
49 – L Orbital gyrus (A13)		* OCD > HC
51 – L Orbital gyrus (A12/47l)		** OCD > HC
52 – R Orbital gyrus (A12/47l)		** OCD > HC
53 – L Precentral gyrus (A4hf)		* OCD > HC
58 – R Precentral gyrus (A4ul)		* OCD > HC
61 – L Precentral gyrus (A4tl)		** OCD > HC
62 – R Precentral gyrus (A4tl)		* OCD > HC
64 – R Precentral gyrus (A6cvl)		* OCD > HC
72 – R Superior temporal gyrus (A41/42)	* OCD > HC	*** OCD > HC
79 – L Superior temporal gyrus (A22r)		* OCD > HC
82 – R Middle temporal gyrus (A21c)	* HC > OCD	* HC > OCD
91 – L Inferior temporal gyrus (A37elv)		* OCD > HC
92 – R Inferior temporal gyrus (A37elv)		* OCD > HC
95 – L Inferior temporal gyrus (A20il)		* OCD > HC
96 – R Inferior temporal gyrus (A20il)	** HC > OCD	*** HC > OCD
100 – R Inferior temporal gyrus (A20cl)		** OCD > HC
101 – L Inferior temporal gyrus (A20cv)		* OCD > HC
102 – R Inferior temporal gyrus (A20cv)		*** OCD > HC
112 – R Parahippocampal gyrus (A35/36c)		* OCD > HC
116 – R Parahippocampal gyrus (A28/34)		* OCD > HC
120 – R Parahippocampal gyrus (TH)		* OCD > HC

124 – R Posterior superior temporal sulcus (cpSTS)	** HC > OCD	* HC > OCD
125 – L Superior parietal lobule (A7r)		* OCD > HC
130 – R Superior parietal lobule (A5l)	** OCD > HC	*** OCD > HC
134 – R Superior parietal lobule (A7ip)	** OCD > HC	*** OCD > HC
137 – L Inferior parietal lobule (A39rd)		* OCD > HC
157 – L Postcentral gyrus (A1/2/3tonla)		* OCD > HC
159 – L Postcentral gyrus (A2)	** OCD > HC	*** OCD > HC
171 – L Insular gyrus (dlg)		* OCD > HC
183 – L Cingulate gyrus (A24cd)		* OCD > HC
184 – R Cingulate gyrus (A24cd)		* OCD > HC
186 – R Cingulate gyrus (A23c)		* OCD > HC
188 – R Cingulate gyrus (A32sg)		** OCD > HC
193 – L Medioventral occipital cortex (cCunG)		** OCD > HC
199 – L Lateral occipital cortex (mOccG)		** OCD > HC
200 – R Lateral occipital cortex (mOccG)	* OCD > HC	*** OCD > HC
205 – L Lateral occipital cortex (iOccG)		* OCD > HC
212 – R Amygdala (mAmyg)		* OCD > HC
229 – L Dorsolateral putamen		* OCD > HC
233 – L Thalamus (mPMtha)		** OCD > HC
240 – R Thalamus (Pptha)		* OCD > HC
245 – L Thalamus (lPFtha)		* OCD > HC
247 – L Subthalamic nucleus		** OCD > HC
Rich-club nodes[2]		
10 – R Superior frontal gyrus (A6m)		** OCD > HC
27 – L Middle frontal gyrus (A10l)		* OCD > HC
37 – L Inferior frontal gyrus (A44op)		* OCD > HC
73 – L Superior temporal gyrus (TE1.0/1.2)		* OCD > HC
77 – L Superior temporal gyrus (A38l)		* OCD > HC
107 – L Fusiform gyrus (A37lv)		*** OCD > HC
135 – L Inferior parietal lobule (A39c)		** OCD > HC
136 – R Inferior parietal lobule (A39c)		* OCD > HC
138 – R Inferior parietal lobule (A39rd)		* OCD > HC
150 – R Precuneus (A5m)		*** OCD > HC
181 – L Cingulate gyrus (A23v)		* OCD > HC
197 – L Medioventral occipital cortex (vmPOS)		* OCD > HC
217 – L Hippocampus (cHipp)		* OCD > HC
220 – R Ventral caudate		* OCD > HC

[1] ID, hemisphere, gyrus and cytoarchitectonic description reported as in the Brainnetome Atlas. [2] Rich-club nodes across all sets considered (top 25% to top 5%). Group comparisons are performed using permutation testing (50,000 permutations of group assignments). The observed difference is calculated as OCD-HC and is assigned a p-value. All reported p-values are FDR-corrected at q = 0.05. *** q < 0.001; ** q < 0.01; * q < 0.05; L: left; R: right; OCD: obsessive-compulsive disorder patients; HC: healthy controls.

Table S3. Partial correlation coefficients between observed effects and clinical characteristics.

		Y-BOCS				OCI-R							
		OBS	***COM***	***TOT***	***DURATION***	***WASH***	***CHECK***	***ORD***	***OBS***	***HOARD***	***NEUTR***	***TOT***	***MADRS***
	Ø	-0.20	0.04	0.06	0.17	0.37	-0.11	0.23	0.02	0.20	-0.11	-0.29	-0.32
	$Ø^w$	0.29	0.55	-0.49	0.15	-0.23	0.29	0.38	0.48	0.12	-0.62	0.04	0.32
Strength	RICH-CLUB	0.20	-0.22	0.05	0.00	-0.12	-0.17	-0.40	-0.06	-0.39	0.15	0.45	0.01
	FEEDER	0.26	-0.17	-0.01	-0.10	-0.05	-0.14	-0.38	-0.08	-0.37	0.20	0.36	0.12
	LOCAL	0.37	0.03	-0.20	-0.09	0.03	-0.08	-0.24	0.04	-0.35	0.04	0.35	0.32
Density	RICH-CLUB	-0.32	-0.55	0.50	0.14	-0.03	-0.37	-0.51	-0.34	0.33	0.46	0.20	-0.60
	FEEDER	-0.18	-0.38	0.33	-0.21	-0.10	-0.39	-0.38	-0.43	-0.19	0.42	0.28	-0.38
	LOCAL	0.20	0.41	-0.36	0.19	0.09	0.37	0.41	0.37	0.11	-0.42	-0.26	0.43

Spearman's rho partial correlation coefficients controlling for age, sex and education.All associated p-values are above 0.05. Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; DURATION: disease duration expressed in years; OCI-R: Obsessive-Compulsive Inventory-Revised; MADRS: Montgomery-Åsberg Depression Rating Scale; Ø: topological rich-club organization; Øw: weighted rich-club organizaton; OBS: obsessions score; COM: compulsions score; TOT: total score; WASH: washing score; CHECK: checking score; ORD: ordering score; HOARD: hoarding score; NEUTR: neutralizing score.

CHAPTER 4

COULD PROTECTIVE MEASURES FOR COVID-19 CONTRIBUTE TO THE WORSENING OF OBSESSIVE-COMPULSIVE SYMPTOMS ?

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Abstract

The COVID-19 outbreak has placed considerable strain on the wellbeing of individuals across the world, and resources have been already put in place to assess the psycho-social aftermath of this pandemic. With strict hygiene measures and recommendations now constituting the norm, we wonder specifically about those individuals that were heavily concerned by contamination, germs and viruses in the pre-COVID era. Patients affected by obsessive-compulsive disorder (OCD), and specifically those of the contamination/washing subtype, might indeed be exceptionally vulnerable to an increase in symptom severity due to the current circumstances. Albeit only relating to the acute phase of this pandemic, evidence collected thus far offer valuable insights into whether this concern is substantiated. After reviewing some of the available results, we reason on the conclusions that we can currently draw, on the factors that might play a role in driving them and on those that might be worth focusing on as the pandemic is running its course.

The advent of COVID-19 posed an unprecedented challenge to the way of living that we have grown to take for granted. The simple behaviors and actions that effortlessly and automatically distinguished our daily interactions with the surrounding environment started to present a threat to personal and societal survival. Our day-to-day reality is now turned into one advocating the need for physical distancing, the use of personal protective equipment, and the exhaustion of precautionary hygiene measures such as washing/disinfecting hands and object items. The fear of being a risk for oneself and others after touching a specific surface or being 1.5 meters too close to another person, came as something new into the world of most. However, for a portion amounting to around 2-3% of the population worldwide (1), these thoughts have represented the norm long before the spread of COVID-19.

The excessive, intrusive worrying or fear of specific circumstances, associated with ritualistic behaviors consequently endorsed to prevent the dreaded event/situation or to reduce the elicited anxiety, are characteristics of obsessive-compulsive disorder (OCD). Albeit the content of obsessions and compulsions can vary considerably across affected individuals, recurrent themes have been identified, with contamination fear and washing/cleaning compulsions being among the most commonly experienced (2).
Pandemics and infectious diseases constitute exceptional circumstances that can render this group of individuals exceptionally vulnerable to an increase in symptom severity, potentially providing them with indisputable evidence that the world is indeed a dangerous place at the mercy of germs and viruses and that only proper, scrupulous hygiene practices prevent diseases of this form from spreading uncontrollably. As a matter of fact, previous outbreaks like Severe Acute Respiratory Syndrome (SARS), Middle East respiratory Syndrome (MERS) and Influenza have witnessed and documented an exacerbation of OCD (3).

Since the classification as a pandemic by the World Health Organization, resources have been trans-geographically put in place to account for the psycho-social aftermath of the COVID-19 outbreak on individuals affected by OCD. A discrete number of studies report various levels of symptoms aggravation already detectable during or following the first wave of the pandemic, ranging from 5% up to 70% among both adult (4-9) and children/adolescents (10, 11) populations. Following the above-mentioned line of reasoning, special attention has been devoted to the contamination/washing subtype, and the link with a greater increase in symptom severity (compared to other obsession and compulsion types) has been in more than one instance established (6, 8). When evaluating beliefs associated with COVID-19, washers agreed more with dysfunctional hygiene-related beliefs (along the lines of “Coronavirus is the result of people being very careless about hygiene”) than non-washers, a factor that positively correlated with worsening of symptoms (6).

Alongside these results however, empirical evidence once more highlights how syllogistically reasoning on the relationship between occurrences is most often, at least partially, inadequate. For example, in a Danish sample of children and adolescents with OCD, contamination fear was not predictive of poorer outcome, but baseline aggressive/sexual obsessions and compulsions were (10). Or else, Chakraborty and Karmakar (2020) (5) surveyed only OCD patients with obsessions related to contamination, and compulsions related to hand washing or cleaning household items, yet reported that only 6% experienced a 5-10% increase in symptoms. Or again, Khosravani et al. (2021) (7) found a significant increase in symptoms common to all, but special to none, symptom dimensions, suggesting that general distress and anxiety rather than specific enforced COVID-19 recommendations might mediate worsening of symptoms, similar to what has been observed in other clinical and non-clinical populations.

Conversely, it is worth noting that a proportion of OCD patients so far maintained a stable symptom status or even experienced an improvement during the pandemic (9, 12). Identifying what makes people thrive on difficult circumstances is instrumental to help those who do not. Hence, we wonder, what lightens in some the increased burden that falls on others?

First, we do not underestimate the impact that the stigma associated with mental illness and consequent isolation from society normally has on individuals affected by this or other psychiatric disorders. In some sense, COVID-19 rendered feelings of impotence, uncertainty or fear universal. This might have given back to OCD patients a sense of belongingness, of being aligned again with the rhythms of the healthy society, potentially amplifying resilience and strengthening mental resources, as suggested already long ago (13). Second, increased free time might provide the opportunity to obsessions and compulsions to thrive even more. In this regard, whether a patient is currently undergoing treatment might make a difference on clinical outcome. Remission status and having concluded the treatment course before the beginning of the pandemic has indeed been associated with more elevated symptom worsening in both adults (8) and children/adolescents (10). Of note, therapeutic approaches have been challenged by the situation in a number of ways. At least for certain periods, they might have stopped altogether, with medical staff being deployed to emergency care and, even when in place, factors like increased stress from both patient and clinician sides, alongside logistic challenges, might have halted the expected progress. This was for example the experience of 137 US clinicians, reporting a worsening of symptoms in 38% of their patients, undergoing exposure and response prevention (ERP) treatment at that time (9). Not only might traditional treatment approaches not be feasibly and effectively implementable during the pandemic, but also a recent consensus paper by the

International College of Obsessive-Compulsive Spectrum Disorders explicitly advised ERP programs to be paused for patients with contamination fear and washing compulsions (14), recommending pharmacological treatment as the first option. Distinguishing compulsive from mindful/responsible hand washing, or obsessive worrying from rational concern can be difficult not only for patients but for clinicians as well, rendering ERP strategies that are meaningful and robust, while being in line with governmental guidance, challenging to design and implement. Enhanced supportive therapies like social and occupational care and immediate access to psychological support might nonetheless be a key distinguishing element allowing a portion of patients to improve regardless of the pandemic. Lastly, we shall not neglect the role of subjectivity that the exclusive use of self-report questionnaires inevitably introduces, recognized as a limitation general to the majority of the studies conducted until now and herein reported.

Altogether, the evidence collected so far does not convincingly ascribe a crucial role to the specific COVID-19 recommendations in driving symptom worsening in patients affected by OCD, nor recognizes individuals of the contamination/washing subtype as being at exceptional risk in the current circumstances. The OCD population as a whole rather demonstrates an increased vulnerability that needs to be carefully addressed, yet without assuming that necessarily all patients will be negatively affected. However, our current understanding, together with the conclusions that we can draw, are limited cross-sectionally in time. Only longitudinal studies will elucidate the long-term sequalae of the COVID-19 pandemic, which could still reveal an increase in OCD symptoms that are centered around the contamination theme. In this regard, we deem especially relevant to document, for example, a switch in main OCD phenotype, or the rise of new obsessions and compulsions related to germs and viruses. Given the history of previous epidemics, we acknowledge the need of extending this latter concern to the general population as well. Alarmingly high prevalence rates of post-traumatic stress disorder, depression and OCD have indeed been documented in severe SARS survivors up to four years after the spread of the disease (15). For the current epidemic, some evidence has been collected already, pointing to an increase in obsessive-compulsive symptoms in populations of adults (16), students (17) and healthcare workers (18). However, with hygiene precautionary measures and social restrictions still heavily enforced on the population, the still standing fine, blurry line separating adaptive from maladaptive responses makes it difficult to undertake any objective assessment. Yet, in light of the evidence at our disposal, we still regard a rise in OCD symptoms and/or diagnoses as a concrete risk, and we thus make it a priority to watchfully evaluate the mental wellbeing of individuals throughout what we can assume will still be a long course of this epidemic.

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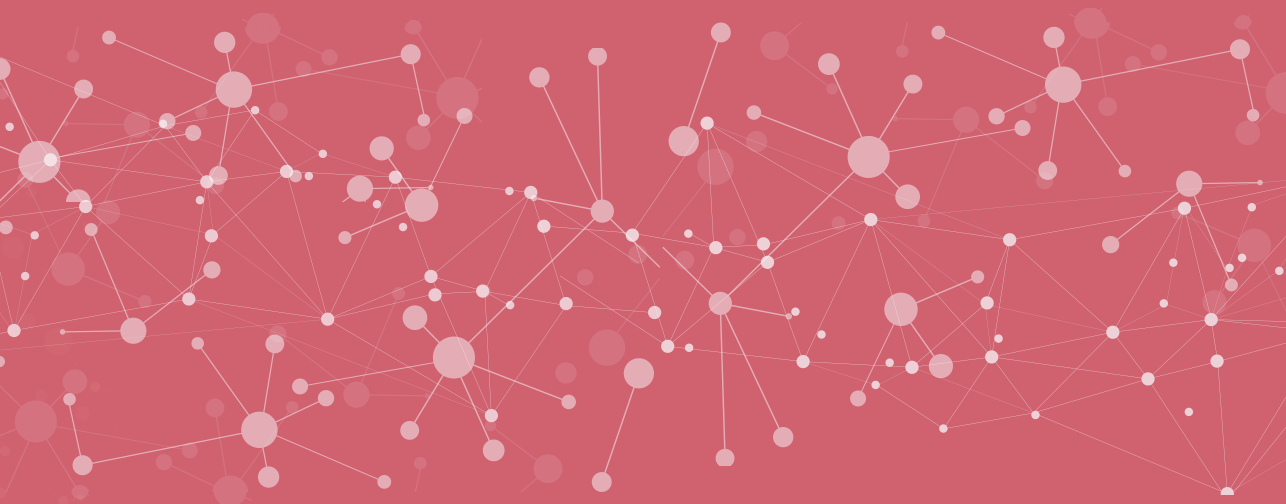
PART 2



CRITICAL CONSIDERATIONS ON BRAIN STIMULATION TREATMENT

CHAPTER 5

THE EFFECTS OF DEEP BRAIN NON-STIMULATION IN SEVERE OBSESSIVE-COMPULSIVE DISORDER: AN INDIVIDUAL PATIENT DATA META-ANALYSIS

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Abstract

Non-intervention-related effects have long been recognized in an array of medical interventions, to which surgical procedures like deep-brain stimulation (DBS) are no exception. While the existence of placebo and micro-lesion effects has been convincingly demonstrated in DBS for major depression and Parkinson's disease, systematic investigations for Obsessive-Compulsive Disorder (OCD) are currently lacking. We therefore undertook an individual patient data meta-analysis with the aim of quantifying the effect of DBS for severe, treatment-resistant OCD that is not due to the electrical stimulation of brain tissue. The MEDLINE/PubMed database was searched for double-blind, sham-controlled randomized clinical trials published in English between 1998 and 2018. Individual patient data was obtained from the original authors and combined in a meta-analysis. We assessed differences from baseline in obsessive-compulsive symptoms following sham treatment, as measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Four studies met the inclusion criteria, randomizing 49 patients to two periods of active or sham stimulation. To preclude confounding by period effects, our estimate was based only on data from those patients who underwent sham stimulation first (n = 24). We found that sham stimulation induced a significant change in Y-BOCS score ($t = -3.15$, $p < 0.005$), lowering it by 4.9 ± 1.6 points [95% CI = (-8.0, - 1.8)]. We conclude that non-stimulation-related effects of DBS exist also in OCD. The identification of the factors determining the magnitude and occurrence of these effects will help to design strategies that will ultimately lead to a betterment of future randomized clinical trials.

1. Introduction

Obsessive-compulsive disorder (OCD) is a highly debilitating neuropsychiatric disorder, affecting around 2% of the population. It is characterized by repeated intrusive thoughts, images or impulses (i.e., obsessions) that cause negative emotion (usually labelled as anxiety) and trigger behaviors aimed at reducing this negative affect (i.e., compulsions) (1). Effective treatment is available in the form of cognitive behavioral therapy (mainly exposure therapy) and pharmacological treatment (mainly with serotonin reuptake inhibitors (SSRIs) and clomipramine) (1). In spite of these treatment options, an estimated 10-20% of affected individuals remains resistant to all therapies, suffers from severe incapacitating symptoms and, consequently, maintains a very low quality of life (2). For this group of patients, the possibility of deep brain stimulation was introduced in 1999, being regarded as an appealing "last resort option" mainly due to its adjustability and reversibility (3). By delivering electrical current to specific locations in the brain, DBS therapy can be tailored to the individual patient's level of complaints, and most stimulation-induced side effects can be minimized by adjusting stimulation parameters (2). The precise mechanism of action of DBS is only partially known, with evidence showing that DBS can exert its effect through both electrical activation and inhibition of brain areas and circuits that are involved in the pathophysiology of OCD (4-6). Alongside numerous uncontrolled case reports, series and trials (7-11), several blinded, randomized controlled evaluations have demonstrated its effectiveness (12-17), using different targets in the brain and leading to US Food and Drug Administration (FDA) and Conformité Européenne (CE) mark approval through a humanitarian device exemption in 2009 (18, 19). A recent meta-analysis reported a response percentage of 60% and a global reduction in OCD symptoms of 45%, along with considerable yet not systematically assessed improvement in some aspects of quality of life (20).

However, as with 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. It has long been recognized that the role of placebo responses is to be taken into account, as the simple act of receiving any treatment can be efficacious by itself and induce clinically meaningful neurobiological changes in an array of human health-related conditions (21). Neurosurgical procedures are no exception to this rule, as was elegantly demonstrated in trials of DBS for Parkinson's disease (PD) (22, 23). These findings confirm the notion that surgical procedures do include a placebo component, mainly mediated by the expectation of benefit that is inherently triggered in the patient. However, obvious ethical issues, mainly about the inclusion of sham surgery, hinder the exploration of the role of placebo in surgical treatments: a sham surgical procedure that

includes administration of anesthetic drugs and inflicting tissue damage is inherently dangerous and therefore generally deemed unacceptable (24, 25).

DBS may be an exception to this rule, as 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 on brain cells and circuits. 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 for several weeks, and then switched to the other condition in the second part of the study. However, this approach is not without problems. So-called 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 (26). 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 (26). Furthermore, it is well-documented that some of the effects and side effects of DBS occur very rapidly (27), thus possibly giving rise to problems with blinding, especially during the second period of the study. 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 (28).

To date, there have been several narrative reviews, systematic reviews and meta-analyses summarizing existing data on the effectiveness and safety of DBS surgery in OCD (20, 28-30). However, none of them explicitly focused on the magnitude of non-stimulation-related effects. This knowledge is not only necessary to design better clinical trials, but can also inform clinical practice on which other elements of the treatment context might be harnessed to reinforce patient's response and motivation. We therefore undertook an individual patient data meta-analysis with the aim of quantifying the effect of DBS for severe, treatment-resistant OCD that is not due to the electrical stimulation of brain tissue. We included all double-blind, sham-controlled randomized clinical trials (RCTs) and looked at changes in clinical symptoms following a period of sham stimulation, while controlling for the occurrence of period effects. Our hypothesis was that a statistically significant non-stimulation effect would exist.

2. Materials and Methods

2.1 Search strategy and study selection

Studies were identified by searching electronic databases and scanning reference lists of relevant papers and reviews. Searches were restricted to human studies published

between 1998 and 2018. This search was applied to the MEDLINE/PubMed database using the following Mesh terms: “Obsessive-Compulsive Disorder” AND (“Deep Brain Stimulation” OR “Electric Stimulation”). Titles and abstracts of all papers identified in the electronic searches were inspected to identify clinical studies on DBS in OCD. The full-text of candidate studies was then obtained to screen for relevance and eligibility.

Studies had to meet the following criteria in order to be included: 1) use of a randomized, double-blind, sham-controlled design; 2) reporting of baseline and post-sham (i.e., post-implantation after receiving sham stimulation) treatment scores on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS); 3) use of unique data; 4) availability of individual patient data; 5) published in English in a peer-reviewed journal. Thus, posters, conference abstracts, case reports, letter to editors and commentaries were discarded. Reference lists of narrative and systematic reviews and meta-analyses were inspected for additional potential sources. Crossover designs consisting of multiple, not-consecutive ON vs. OFF stimulation blocks were excluded.

2.2 Data extraction and quality assessment

Information was extracted from each included trial on: 1) patient characteristics (including age, gender, illness duration and severity); 2) design characteristics (including duration of optimization phase following surgery, duration of stimulation arms, presence and duration of a washout period); 3) surgical target for electrode implantation; 4) outcome measures and 5) number of dropouts.

The primary outcome was the effect of sham-stimulation on OCD symptoms according to changes in Y-BOCS scores. The Y-BOCS is the most widely used, validated OCD rating scale (31), with scores ranging from 0 (no symptoms) to 40 (extremely severe OCD symptoms). Individual patient data was used instead of pooled averages. In studies where Y-BOCS scores were grouped per condition, individual data was retrieved by contacting the original authors. All but one responded and provided the raw data that was then used for the analysis.

Each study was independently evaluated to ascertain the validity of the included RCTs. According to the Cochrane methods, the risk of bias was categorized as high, low or unclear on the adequacy of randomization, concealment of allocation and blinding of participants, personnel and outcome assessors.

Eligibility assessment, study selection and data extraction were performed by three independent researchers (S.B, L.G and T.vdH), and all discrepancies were resolved by re-checking and further discussing source papers between reviewers.

2.3 Statistical analysis

Analyses were conducted using R (32). As our primary outcome measure, we computed individual change scores by subtracting the baseline Y-BOCS from the post-sham Y-BOCS score. In order to ensure the highest possible level of homogeneity of the data, baseline was defined as the last Y-BOCS measurement before implantation. We first evaluated the relationship between the baseline and post-sham Y-BOCS score by computing Pearson's correlation and intraclass correlation (ICC) estimates separately for the two order conditions. The R packages "*lme4"* (33) and "*lmerTest"* (34) were then used to perform linear mixed effects analyses. We tested for period effects (OFF-ON vs. ON-OFF) by including data from both periods and entering order of stimulation arms as a fixed effect into the model. Random intercepts for the included studies were added to the model. Should an order effect be detected, the analysis was confined to data derived from the first crossover period, thus including only those patients who underwent sham stimulation first (i.e., OFF-ON). P-values of the fixed effects were determined using the Satterthwaite's degrees of freedom method, as implemented in *lmerTest*'s ANOVA function. This approach was chosen because it was shown to produce more acceptable Type I error rates even for smaller sample sizes as compared to more commonly used methods for evaluating significance such as likelihood ratio tests or the t-as-z approach (35).

3. Results

3.1 Study characteristics

In the initial electronic searches, 272 studies of interest were found. Snowball searching of reference lists of relevant papers and reviews identified an extra 6 studies, yielding a total of 278 records of which titles and abstracts were screened (**Figure 1**). Of these, 42 full-text articles were deemed potentially relevant and were assessed for eligibility. 38 studies were excluded, mainly because they did not include a sham procedure (n = 20), or focused on outcomes or effects of DBS that differed from those of interest for the present study (n = 10). Others only included follow-up data (n = 3), failed to report Y-BOCS scores (n = 1) or did not present unique data (n = 2). One of the excluded studies was a double-blind, sham-controlled trial, in which patients were randomized to multiple, separate periods of active vs. sham stimulation. However, the exact order of stimulation arms was not reported for all patients (12). A last eligible study was excluded because the authors did not react to our request to provide the individual data (14).

Four studies were finally included in the analysis, all of them being double-blind, sham-controlled RCTs assessing the efficacy of DBS for primary, treatment-resistant OCD (13, 15-17). The included studies provided data for a total of 49 patients,

who received DBS in the subthalamic nucleus (13), the nucleus accumbens (15), the anterior limb of the internal capsule (16, 17) or the bed nucleus of the stria terminalis (17). All studies included patients aged between 18 and 65 years, suffering from severe OCD (i.e., Y-BOCS score of at least 25) for at least 5 years and meeting stringent criteria for refractoriness to treatment (36). **Table 1** summarizes the main design characteristics of the included studies. Three comprised an open, exploratory period for optimization of the stimulation parameters before entering the double-blind randomized phase (13, 16, 17). Three studies adopted a crossover design, with duration of the stimulation arms of 3 months (13, 15, 17). Of these, only one study applied a washout period lasting 1 month (13), whereas in the others the crossover to the second stimulation condition happened consecutively. One of the included studies adopted a staggered-onset design (16). That is, at 30 days post-implantation, half of the patients were assigned to sham DBS for 30 days prior to active DBS (OFF-ON), whilst the others were assigned to active DBS straightaway (ON-ON).

In all studies, allocation to active and sham treatment was determined by randomization, albeit only one adequately reported on the method used for sequence generation and allocation concealment (13). Blinding of assessors and patients was preserved at least until the end of the crossover phase in all studies. However, none of them reported on formal testing on the effectiveness of blinding, and only three studies at least addressed the issue in their discussion (13, 15, 17). Whereas unblinding might have been prevented by the use of either fixed (15) or below the side-effects threshold (13) stimulation parameters, this might have not been the case when a relatively extensive optimization phase was performed (16, 17).

Table 1. Study characteristics.

Authors	Patients	Age	DBS target	Design	Optimization	Arm duration	Wash-out	Drop-out
Mallet et al. (2008)	17	43.05 (±7.9)	STN	Crossover	3 months	Two 3-months periods	1	1
Goodman et al. (2010)	6	36.2 (±8.6)	ALIC	Staggered-onset	30 days	Two 30-days periods (OFF-ON) vs. 60 days (ON-ON)	No	0
Huff et al. (2010)	10	36.3 (±6.4)	Right NAc	Crossover	No	Two 3-months periods	No	0
Luyten et al. (2016)	17	38.7 (±10.9)	ALIC/BNST	Crossover	9 months (average)	Two 3-months periods [a]	No	0

[a] An escape procedure was established in case of unbearable worsening of symptoms during the blinded phase. Median duration of the ON phase (89 days) was longer than that of the OFF phase (44 days). STN = Subthalamic nucleus, NAc = Nucleus Accumbens, ALIC = Anterior Limb of the Internal Capsule, BNST = Bed Nucleus of the Stria Terminalis

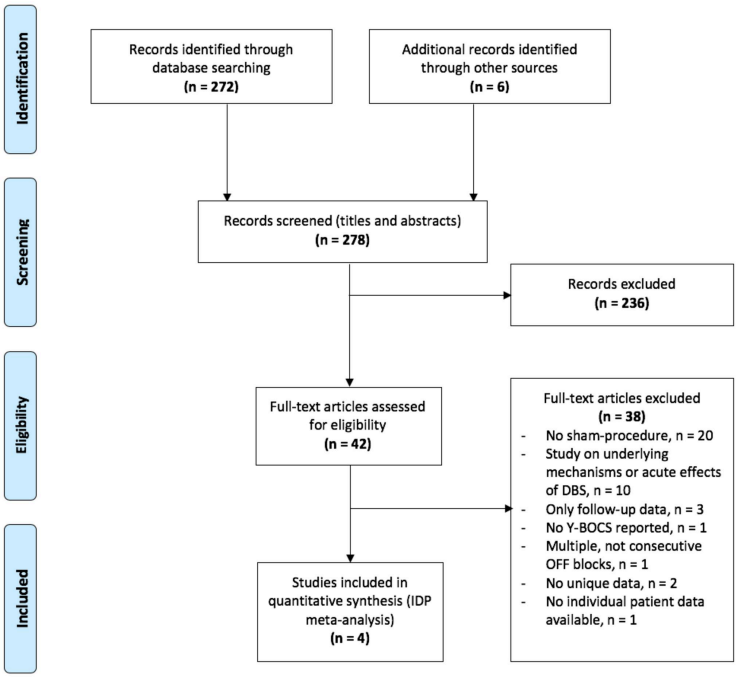

Figure 1. Flow of information according to PRISMA statement, study selection and reasons for exclusion.

3.2 Post-sham stimulation outcome evaluation

Individual patient data was available for all four trials, randomizing 49 patients to two periods of either active or sham stimulation. Data from 3 patients who did not undergo a period OFF stimulation were excluded from the analysis (16).

We first investigated the occurrence of period effects by assessing the relationship between baseline and post-sham Y-BOCS score separately for the two order conditions. Graphical exploration of this relationship showed larger drops in Y-BOCS score for the OFF-ON (mean = -4.91, SD = 7.65) as compared to the ON-OFF condition (mean = -1.77, SD = 5.38) (**Figure S1**). This was also reflected by larger Pearson's correlation and intraclass correlation (ICC) estimates for the ON-OFF condition (r = 0.50, ICC = 0.45) than for the OFF-ON condition (r = 0.3 9, ICC = 0.07).

We then formally tested for period effects by fitting a linear mixed effects model to data from both periods (n = 46). Visual inspection of residual plots did not reveal any conspicuous deviations from homoscedasticity or normality. Following a period OFF-stimulation, the Y-BOCS score lowered by 4.52 ± 1.73 [95% CI = (-7.90, -0.67)], constituting a marginally significant change (t = -2.60, p = 0.0580). The order of stimulation arm did not have a significant influence on Y-BOCS score reduction (b = 3.46, SE = 1.91, t = 1.80, p = 0.078).

However, in light of the relatively small sample size, the relatively large size of the coefficient for the period effect and the above-mentioned risk of unblinding, we decided to base our estimate on the data from the OFF-ON condition only (n = 24). The mean Y-BOCS scores at baseline and post-sham were respectively 33 (SD = 3) and 28 (SD = 8) points (**Figure 2**). The mixed effects model fitted to these data showed that sham stimulation induced a significant change in the Y-BOCS score (t = -3.15, p = 0.0045), lowering it by 4.91 ± 1.56 points [95% CI = (-8.03, -1.79)].

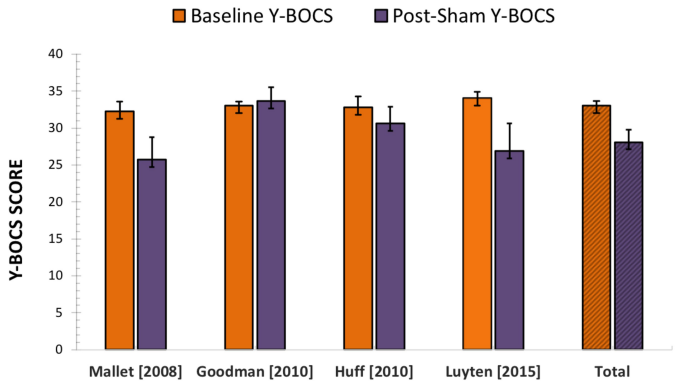

Figure 2. Mean Y-BOCS scores at baseline and post-sham stimulation with their respective standard error of the mean (SEM), plotted for the included studies and the pooled individual data (n = 24). Only data of patients who entered the sham condition first is shown.

4. Discussion

The present study shows, using individual patient data from published randomized controlled trials, that DBS for treatment-refractory OCD involves a statistically significant "non-stimulation" effect, thus confirming our initial hypothesis. The data are suggestive of a period effect: albeit not statistically significant, the recorded smaller drops in Y-BOCS score in the ON-OFF condition might be suggestive of ineffective blinding, with patients being more or less aware of the clinical effects of active stimulation. Thus, in the attempt of reducing the risk of underestimating the magnitude of a non-stimulation related effect, we decided to base our estimate on data from the OFF-ON condition only. The average difference in Y-BOCS score between baseline and post-sham stimulation amounted to about 5 points or 14.9%, which constitutes a meaningful difference in clinical terms (37).

To our knowledge, this is the first study to explicitly examine the non-stimulation related effects of DBS in OCD. There are however some studies exploring the clinical effect of expectation in DBS of the subthalamic nucleus (STN) for

Parkinson's disease that can be informative here. Two of those reported that blinded assessment of treatment was associated with a smaller clinical effect compared to unblinded assessment (23, 38). In a third study, a positive versus negative expectation bias was purposely induced. It was found that hand movement following STN stimulation was faster when patients expected good motor performance than when they did not (39). Finally, in a post-hoc analysis of a large crossover DBS study for Parkinson's disease (40), it was stated that patients who first entered the OFF condition showed better response to active-DBS than vice versa [(41), but see (42)]. Together, these studies clearly indicate that expectations can influence the effects of DBS.

Regarding the magnitude of this effect and its clinical significance in psychiatric disorders, the "Reclaim" (43) and "Broaden" (44) DBS trials for depression can be informative, as in both these studies attention was given to a possible placebo effect from the outset. In the "Reclaim" trial, the response rate in the sham group was estimated at 15% and turned out to be 14.3%. In the "Broaden" study these respective figures were 18.5% and 17%. Although OCD is suggested to be less prone to placebo effects than depression (45), these numbers are in line with the findings of the present study.

Several factors may influence the occurrence and magnitude of expectation effects. First, the length of the post-surgery optimization phase might play a role. It can be hypothesized that the less time between lead placement and start of the blinded crossover phase, the stronger the expectation may be, reflecting the hope patients might have for improvement through a treatment applied in the foreseeable future. On the other hand, a long period with elaborate testing of the ideal study parameters is likely to give patients the chance to figure out what effects (wanted or unwanted) are associated with the stimulation being "ON", thereby increasing the risk of effectively unblinding the period after randomization (25). Similarly, it might be the case that placebo responses could be smaller for long periods of sham stimulation. Although not explored in the context of DBS, continuation studies in clinical trials of antidepressants indeed suggest that placebo effects are not sustained long-term, demonstrating the superiority of continued medication over prolonged placebo treatment in preventing symptom reoccurrence (46). Another factor that may be tightly related to expectation effects is the probability of receiving the active treatment. When analyzing clinical outcomes of DBS in PD patients over the course of 6 months, Goetz et al. (47) reported increased odds of placebo responses in trials where the probability of receiving the active treatment was 50% compared to when the probability was lower. A subsequent study from Lidstone et al. (48) registered placebo responses specifically when the stated probability of receiving active medication was 75% but not when it was lower, thus demonstrating the capacity of verbal instructions to modulate clinical effects. This has important implications for the design of clinical trials, in that the magnitude of expectation effects could be

monitored by manipulating the quality of the information given to the patient, e.g., in regard to the probability of receiving active-DBS.

Closed-loop stimulation may provide a possible way forward by reducing the expectation-induced therapeutic benefit. Closed-loop DBS uses a brain-computer interface that provides stimulation upon detection of an abnormal state in the brain, thereby rendering the procedure adaptable to disease fluctuations without the patient being explicitly aware of its functioning (49). Valuable biomarkers and tangible therapeutic effects have been found for neurological conditions such as epilepsy and Parkinson's disease (49). Recent advances in the development of closed-loop devices for the treatment of refractory depression (50) make this a promising avenue for the treatment of psychiatric conditions as well. However, before closed-loop stimulation can be considered a concrete option, a great deal of effort first has to be devoted to the identification of reliable and independent biomarkers for such a complex disease as OCD. Some promising steps have already been taken in this direction in rats (51) as well as patients (52).

Apart from expectation, non-stimulation-related effects also include the so-called "micro-lesion" effect: the placement of the DBS lead with a section surface of around one square millimeter causes a small lesion that can have a clinical effect in itself. Stereotactic lesions have been used for decades in the treatment of severe OCD. Although no direct head-to-head comparison studies are available, their efficacy seems roughly equivalent to treatment with DBS (53). Lesions that are made with therapeutic aim typically have a volume of several cubic millimeters (54), (55) and are therefore considerably larger than those made by the placement of a DBS lead. Nevertheless, a therapeutic effect of such a small lesion cannot be excluded, especially given the relatively small volume of the targeted anatomical structures in OCD (STN: varies between 180-720mm^3, NAc: 433±100mm^3, BNST: 190mm^3). The matter has not been investigated in OCD, but studies in Parkinson's disease convincingly showed the existence of a micro-lesion effect on motor symptoms such as tremor, rigidity, and bradykinesia (56-58), as well as on cognitive functions or on emotion recognition (59-61). Interestingly, several of those studies report that the micro-lesion effect occurs immediately and is detectable until 6 or even 12 months after surgery, indicating that a transitory effect is highly unlikely.

Although systematic investigations are yet to be conducted, the existence of this effect in OCD cannot be ruled out given the indications from the above studies in Parkinson's disease and the history of lesion studies in OCD. In order to design clinical trials that can profitably evaluate DBS efficacy, the magnitude and occurrence of micro-lesion effects are to be pinpointed independently from the effects induced by the expectation of benefit. Having been defined as the "highest quality prospective data

available on the lesion effect in PD" (25), the study by Okun et al. (57) can provide useful pointers in this regard. In this open-label trial, 25% of patients were activated during the first 3 months, while the rest remained without activation constituting a "pure lesion group". If patients are indeed explicitly aware that the stimulation is OFF, then the expectation of a benefit is likely reduced to the minimum or even eliminated, and eventual improvements in symptoms could be ascribed to the micro-lesion only. It is also suggested that findings of possible micro-lesion effects at 6 months post-implantation are not necessarily an index of persistence, but could also be due to insufficiently long medication or stimulation washouts before testing (25). Thus, follow-ups at more than 3 months could be done to assess the duration of these effects by ensuring sufficiently long washout periods.

The present results must be considered and interpreted within the framework of some limitations. Our study pooled individual patient data from existing RCTs to obtain an estimate of non-stimulation-related effects in DBS trials. This approach might be questionable, given that some design characteristics differed across studies. However, statistical analysis with mixed modelling demonstrated that only a small portion of the variance was explained by between-study differences, which likely did not introduce substantial heterogeneity. Thus, we believe that pooling data of different studies allowed us to estimate the effect of interest with more precision than is possible in a single study, even more so when facing the issue of small sample sizes. Caution must be taken in the interpretation of the results also in light of the varying quality of the included studies, especially in regard to blinding of participants. Potential unblinding might indeed have occurred in some studies due to the use of a prolonged post-surgery optimization phase. Finally, we limited our analysis to RCTs published in English in peer-reviewed journals, thus possibly introducing a publication and language bias.

5. Conclusions

In conclusion, non-stimulation-related effects of DBS do exist also in OCD, and need to be addressed in future clinical trials. A careful evaluation and handling of variables like verbal instructions, allocation type (masked vs. unmasked) and length of the optimization phase will allow an informed management of expectation-induced effects. Concurrently, studies aiming to pinpoint the magnitude and duration of micro-lesion effects will progressively lead to the betterment of randomized controlled trials, which will then succeed in disentangling stimulation-related therapeutic benefit from that due to non-stimulation-related factors.

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Supplementary Material

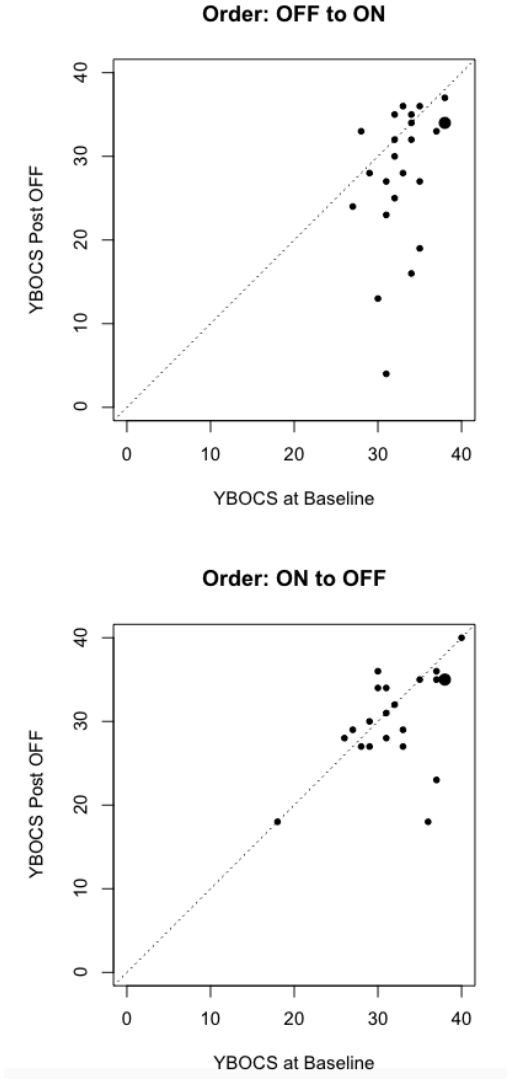

Figure S1. Scatterplots of baseline Y-BOCS score against Y-BOCS score post-sham stimulation for the two order conditions: OFF-ON (n = 24) vs. ON-OFF (n = 22).

CHAPTER 6

DEEP BRAIN STIMULATION-RELATED EXPERIENCES IN OBSESSIVE-COMPULSIVE DISORDER: IN-DEPTH INTERVIEWS WITH OPERATED PATIENTS AND RELATIVES

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Abstract

Deep brain stimulation (DBS) is an effective intervention for refractory obsessive-compulsive disorder (OCD). Although treatment success is measured by a decrease in the severity of core symptoms, this procedure can have broader psychological and physical effects. The field regrettably still lacks knowledge and tools allowing an adequate understanding and assessment of the full range of experiences that accompany DBS treatment. We aimed to describe possible side effects of DBS treatment as experienced by patients, beyond specific changes in OCD core symptoms. We interviewed sixteen patients and seven of their relatives from two independent cohorts, receiving stimulation in different anatomical locations. We conducted semi-structured interviews, transcribed at verbatim. Content analysis was then performed. Our results point to long-lasting positive changes often manifesting as improved mood and calmer behavior, but also negative changes such as impaired memory, concentration and sleep problems. Further, a wide variety of individual experiences were described, suggesting that patients can feel and behave significantly different towards themselves and others, feeling more sensitive, more or less emotional, more impulsive, more irritable, more talkative. We discuss our findings within the framework of existing literature, and stress the importance of accumulating knowledge of the full range of DBS-related experiences, to improve shared decision making between patients and treating clinicians, and to facilitate comprehensive monitoring throughout the course of treatment.

1. Introduction

Deep brain stimulation (DBS) is a promising, last-resort option for treatment-resistant obsessive-compulsive disorder (OCD) patients. Several open-label and randomized controlled trials have been performed to test the efficacy and effectiveness of the procedure, with literature reporting more than 300 operated patients worldwide (1). More than twenty years of experience after the first implantation in 1999 (2) have demonstrated that the benefits of DBS outweigh its risks. Several meta-analyses report a stable reduction of around 47% in the severity of obsessions and compulsions, in up to 70% of patients in the long term (1, 3-5). DBS effects are standardly and primarily assessed as percentage changes in the amount of experienced OC symptoms as measured by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), setting the threshold of clinical response to a reduction of at least 35% on this scale (6). Secondary outcomes include improvement in depressive and anxiety symptoms and global functioning, as measured by an heterogeneous set of standardized scales across studies (1). However, a few lines of evidence (7, 8) suggest that DBS can have much broader effects on the life of patients.

One third of all patients experience adverse side effects (3, 9), mainly reported as mild and transient, resolving upon adjustment of stimulation parameters (1). However, only a minority of published studies explicitly report on side effects (10, 11), and attempts at categorizing different occurrences are often done a posteriori via systematic reviews of the literature (1, 3-5, 12, 13). Additionally, many aspects of the patients' experience and quality of life following surgery are not adequately captured by commonly used questionnaires. Only few attempts have been made to expand on this knowledge using alternative research methods, in the form of in-depth, semi-structured interviews with operated patients (7, 8). These studies suggest that DBS has pervasive effects extending well beyond a hoped-for change in obsessions and compulsions, with patients reporting changes in self-reliance, self-competence, mode of engagement and attitude towards others and towards things in general (7). Knowledge on both the positive and negative changes that DBS treatment can entail is relevant, to neurosurgeons, psychiatrists, psychotherapists and, most importantly, to the patients who consider undergoing surgery (14). However, given that no systematic assessment of immediate and especially of long-term DBS related experiences is available, more research directed at this issue is needed.

In the present study, we aimed to expand the current knowledge on OCD patients' experience of DBS. By means of semi-structured interviews, we investigated their experiences and that of their relatives in the context of two different cohort studies focusing on the ventral capsule/ventral striatum (VC/VS) and bed nucleus of the stria

terminalis (BNST). We aimed to categorize both positive and negative changes, beyond specific effects on OCD core symptoms.

2. Materials and Methods

2.1. Participants

Treating psychiatrists (K.S. and C.B.) approached all patients that received DBS treatment for primary, treatment-refractory OCD, operated at Maastricht University Medical Center (MUMC+, The Netherlands) between 2018 and 2021 (n=17), and the University Hospitals Leuven (UZ Leuven, Belgium) between 2013 and 2021 (n=11). No exclusion criteria were applied in the selection of the sample. Of the patients approached, 16 in total agreed to participate (mean[±SD] age: 44.10[±10.82], 8 males). Eleven patients (47.11[±12.50], 6 males) were operated in the MUMC+ and had the DBS electrodes implanted in the VC/VS. Five patients (age: 46.59[±6.02], 2 males) were operated at UZ Leuven, with the electrodes implanted in the BNST. Information on current medication and comorbidity was obtained from contact with treating psychiatrists and medical files (**Table 1**). Relatives were approached upon consent of the included patients. Five relatives from the MUMC+ cohort and two relatives from the UZ Leuven cohort agreed to be interviewed. All patients and their participating relatives provided written informed consent.

2.2. Data collection

With all participants, a semi-structured interview was held lasting approximately 50-60 minutes, during a single online contact. All interviews were conducted in Dutch by E.V and J.B and were audio-recorded. Using a topic list, we started from open-ended, predetermined questions addressing the patients' OCD and experience with DBS treatment. Depending on what participants spontaneously reported, more specific questions were asked to obtain detailed information. Interviews with the relatives were conducted following the same topic list, but focusing only on the noticed DBS effects (see **Table S1**).

2.3. Data analysis

All interviews were transcribed verbatim using the Otranscribe toolbox (www.otranscribe.com), and analyzed within Kwalitan (v7, www.kwalitan.nl). We performed inductive content analysis (15), first identifying the smallest units of text containing meaningful information, reported with the participants' own words, and then summarizing them in codes generated inductively from the data. Codes referring to a common theme or theoretical construct were grouped and assigned to specific

conceptual categories. This process resulted in the generation of a code tree, created through regular discussions among S.B., E.V., J.B., L.G., K.C., and K.S., resolving disagreements with adjustments to categorization and code tree structure. Only the experiences reported by relatives that were not mentioned by the patients themselves were included in the code tree to avoid duplicate data.

Table 1. Demographic and clinical characteristics.

	MUMC+ **n = 11**	**UZ Leuven** **n = 5**
Sex (% male)	6 (54.5%)	2 (40.0%)
Age[1]	47.11 (±12.50)	46.59 (±6.02)
Years with DBS[1]	2.20 (±1.24)	4.28 (±4.28)
DBS site	VC/VS	BNST
Comorbidity		
Depression	6	1
Anorexia nervosa	1	0
PTSD	1	0
Panic attacks	0	1
Schizophrenia	1	0
ADHD	1	0
MELAS	0	1
Current psychotropic medication		
No medication	3	2
SSRI	1	0
SSRI + antipsychotic	0	1
Clomipramine	1	0
Clomipramine + antipsychotic	1	0
Benzodiazepine	2	1
SSRI + benzodiazepine	1	1
Clomipramine + benzodiazepine	1	0
Antipsychotic + benzodiazepine + SSRI + amphetamine	1	0

[1] Indicated in years, mean (± standard deviation). MUMC+: Maastricht University Hospital; UZ Leuven: University Hospitals Leuven; DBS: deep brain stimulation; VC/VS: ventral capsule/ventral striatum; BNST: bed nucleus of the stria terminalis; PTSD: post-traumatic stress disorder; ADHD: attention-deficit hyperactivity disorder; MELAS: Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes; SSRI: selective serotonin reuptake inhibitors; NA: not available.

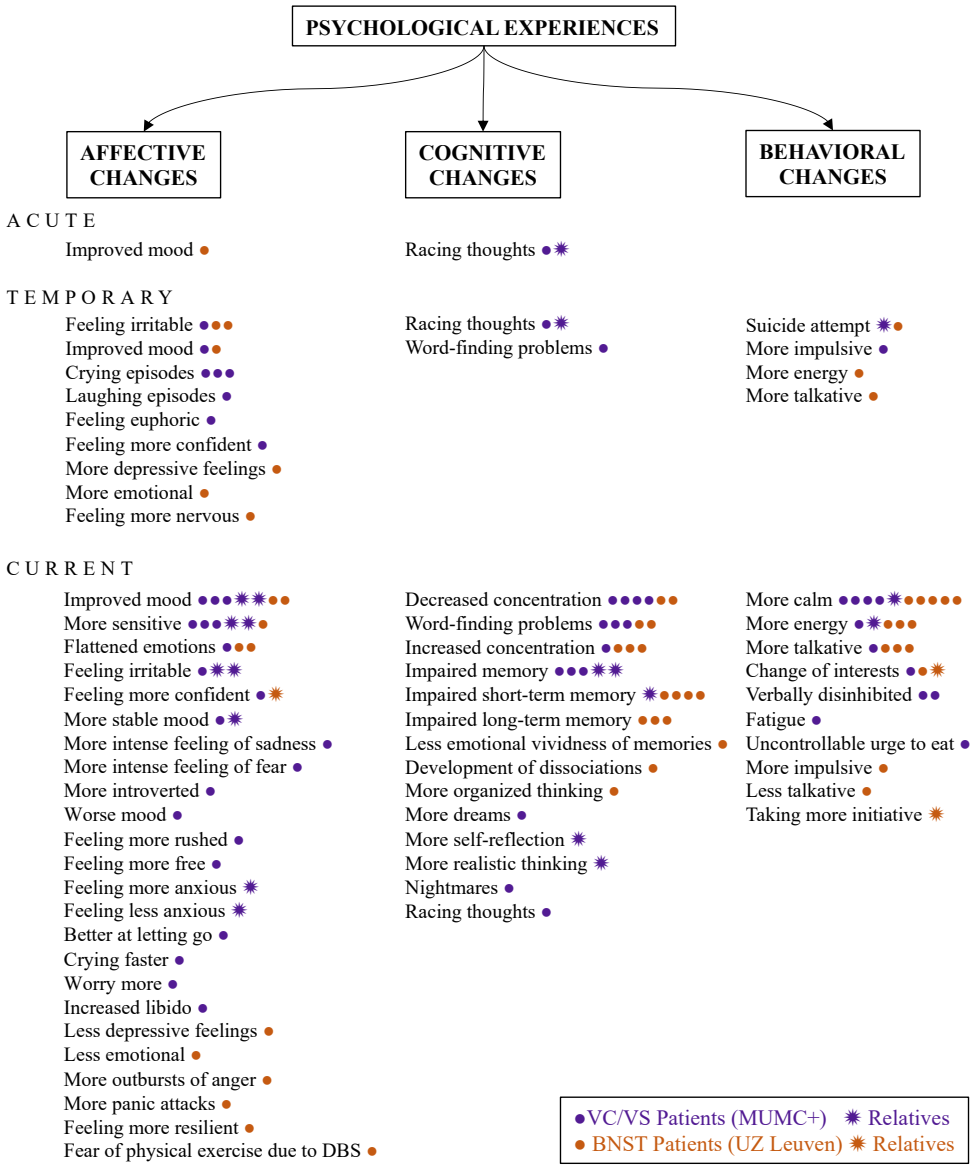

Figure 1. Overview of acute, temporary and current psychological experiences across patients (VC/VS n=11; BNST n=5), based on self-report (•) or on what was reported by a relative (*). VC/VS: ventral capsule/ventral striatum; MUMC+: Maastricht University Medical Center; BNST: bed nucleus of the stria terminalis; UZ Leuven: University Hospitals Leuven.

3. Results

DBS-related experiences were categorized as psychological or physical changes. Within each of these two categories, the reported experiences could be classified according to their duration, as acute (i.e., lasting from a few minutes to hours after adjusting the stimulation protocol/parameters), temporary (i.e., persisting for a certain period, ranging from days to months, but disappeared by the time of the interview), or current (i.e., still present at the time of the interview). In the next sections, we report on the identified categories, while **Figure 1** and **Figure 2** report detailed information about the frequency of the reported experiences across patients.

3.1. Psychological experiences

We defined psychological experiences as changes in affect, cognition or behavior, not including effects on core OCD symptoms (**Figure 1**). Impaired memory (n=13 patients), calmer behavior (n=10) and improved mood (n=10) were the most frequently reported experienced changes.

Affective changes. Improved mood was overall the most commonly reported experience within this category, mentioned by one patient as acutely occurring (*"when increasing the parameters, I always immediately had a pleasant feeling, which meant that my mood was immediately better"*), by two other patients as temporary, and by five patients (and the relatives of two others) as being stable at the time of interview. Similarly, one patient reported less depressive feelings, while more stable mood was described by one patient and another patient's relative. Positive mood changes however did not occur homogenously across patients, and occurrences of a temporary increase in depressive feelings ("*I felt very depressed in the months after the operation"*) and currently experienced worsening in mood were reported.

We additionally recorded varied changes in the experience of different emotions. Four patients and the relatives of two other patients broadly reported feeling more sensitive (*"Because of DBS, I started to feel"*), with individual current occurrences of more intense feelings of sadness, of fear and anger. We additionally recorded instances of more frequently and rapidly occurring crying or laughing episodes for a period after the operation (*"crying very quickly, very tearful, crying about everything, yes I could cry about everything right after the operation"*), of temporarily feeling more emotional or euphoric (*"I felt euphoric for two months, I felt this was manic"*). A few patients and relatives also reported temporary as well as current irritability and current feelings of being rushed (*"I'm very hurried, rushed with everything, more than before the DBS"*), nervousness and worries. One patient reported an increased number of panic attacks, while the relative of another patient reported increased anxiety since starting the DBS

treatment. However, changes in the experience of emotions extended to the positive domain as well, with both temporary and current reports of feeling more confident (*"I was totally convinced of myself"; "I started to feel more and more confident with the DBS"*), more free, more resilient, better at letting go and of increased libido. The relative of one patient reported a noticeable decrease in anxious feelings.
Of note, opposite to these experiences of increased sensitivity, three patients reported current flattened emotions, and one reported feeling less emotional.

Cognitive changes. In several cases, DBS therapy was accompanied by changes in memory, concentration, perception and thinking. Impaired memory was the most commonly reported side-event. Three patients and two relatives noted general memory problems, lasting to date. One patient specifically mentioned current impairments in short-term memory (*"my short-term memory was perhaps better before the DBS"*), while three others reported both short-term and long-term memory problems (*"yes, that is a disadvantage of the DBS, for example, I sometimes forget appointments, they are in my diary, yet I forget them"*). Five patients reported that they were still now experiencing word-finding problems ("*then you are talking and all at once you can't find a word, that sort of thing, I have that very often"*), while in one instance this was only temporary (*"when I had just been discharged from the hospital and the DBS was already on, I think I did have some word-finding problems... but not after that"*).
Changes in concentration were also common, manifesting both as a decrease, as reported by six patients, or an increase, as reported by four other patients.
We additionally recorded a few singular experiences. One patient referred that she was now experiencing her (traumatic) memories less vividly ("*because of the DBS system, those visual images of the past are just gone at once, it seems that they are more in the background. And I still remember them, but the things from the past are a bit more attenuated"*). Another patient recalled the occurrence of dissociations since starting DBS treatment (*"I have also had those dissociations since the DBS... that feels exactly like a psychosis, I had the feeling as if I were in a computer game and looking down on myself and that everything was so unreal, that I was just living in a dream"*). Two patients reported dreaming more, and specifically having more nightmares.
Finally, we recorded a few instances of racing thoughts, occurring as an acute (*"I get restless in my head when the settings are adjusted"*), temporary (*"I had that inner restlessness again with certain parameters"*) or current experience (*"I feel mentally more restless"*). On the other hand, one patient reported more organized thinking ("*I can think more realistically, before the DBS I wasn't able to see the big picture and now I can. Now it's more like 'OK, this is the problem, and this is how we're going to solve it'. I have more overview. I can think more clearly, there is less chaos in my head"*). More

realistic thinking and self-reflection were also recognized by two relatives, albeit not mentioned by the patients themselves.

Behavioral changes. Calmer behavior was the most common experience, reported as a current occurrence by a total of 9 patients and the relative of a tenth patient. Further, four patients and the relative of a fifth patient mentioned a long-lasting increase in energy (*"I am energetic since the operation. I am like an energy bomb"*), while for one patient this effect was only transient and had already vanished by the time of the interview (*"my energy was very high after the operation"*). Two patients also mentioned an increase in impulsivity, which had lasted for several months in one case (*"at the beginning I was very impulsive, I went out and bought all kinds of expensive things. I had taken out a 30'000-euro loan for a car…I was very impulsive in the beginning in terms of buying things"*) or to the date of the interview in the other. Five patients mentioned being more talkative, in one case only temporarily. We recorded single instances of reduced verbal inhibition and of an uncontrollable urge to eat, and the relative of one patient reported that he was taking more initiative. We also recorded instances of opposite experiences, with one patient's report of being less talkative, and one patient currently experiencing fatigue.

Two patients and the relative of a third patient also reported a noticeable, long-lasting change of interests (*"I suddenly have no interest in watching TV at all. I don't watch TV at all anymore, I only listen to the radio"; "Other kinds of interests...since the operation, all at once I started liking other kinds of films, I started liking other kinds of clothes, I started liking other kinds of women"; "Crosswords and watching the news, she didn't do that before the DBS, and now suddenly she does"*).

We recorded two instances of attempted suicide in the period after the operation. In the case of one patient, the attempt took place around 3 months after the operation, ascribed by the patient themself to medication discontinuation prior to the operation. After a brief hospitalization, the strength of the stimulation current was increased, resulting in an almost immediate mood improvement. The second instance of suicide attempt was reported by the relative of one patient (but not by the patient themself). In this case, a 15-year history of depressive symptoms and several suicide attempts before the operation was reported.

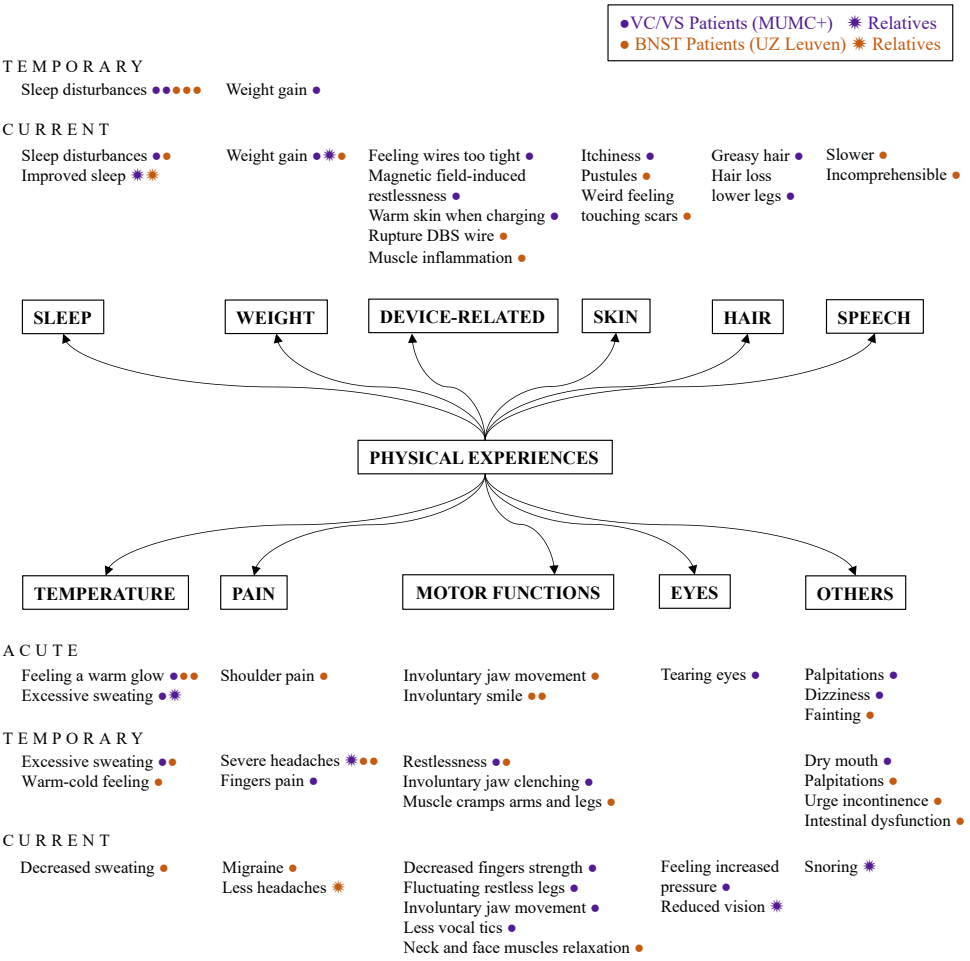

Figure 2. Overview of acute, temporary and current physical experiences across patients (VC/VS n=11; BNST n=5), based on self-report (•) or on what reported by a relative (*). VC/VS: ventral capsule/ventral striatum; MUMC+: Maastricht University Medical Center; BNST: bed nucleus of the stria terminalis; UZ: University Hospitals Leuven.

3.2. Physical experiences

We distinguished physical experiences as changes in body temperature, sleep, pain, weight, motor functions, skin, eyes, hair, speech, device-related side-effects and other (**Figure 2**). Sleep disturbances (n=7), excessive sweating (n=4), headaches (n=4) and weight gain (n=4) were the most frequently reported.

Body temperature. Changes in perceived body temperature primarily accompanied the adjustment of stimulation parameters. Three patients reported feeling

a warm glow through their body, while excessive sweating was mentioned both as acute (*"I did sweat when the DBS was being set up, yes, I had moments when he turned it up really high and I started to sweat"*) and as temporary experience (*"I had to change clothes four times a day, sweat spots from here to here, all sweaty and hot, I was like a stove inside"*). Conversely, one patient reported currently sweating less, while another mentioned temporarily suffering from a "warm-cold feeling" (*"no matter what temperature it was, I could suddenly start shivering and it would last for twenty minutes. And then there were really chills running down your back, just as if you were starting to get a fever"*).

Sleep. Seven patients reported sleep disturbances, manifesting mainly as difficulties falling asleep or reduced amount of sleep. In five patients, these problems disappeared after a few months (*"I only slept 35 minutes a night…from the moment it was implanted, I couldn't sleep"; "I slept 3 hours a night, for months"*), lasting to date for two other patients (*"since the DBS I sleep very badly").* We however also recorded instances of improved sleep, as mentioned by the relatives of two patients (but not the patients themselves).

Pain. Severe headaches were primarily registered among patients from the UZ Leuven cohort, occurring both temporarily after the operation *("in the hospital after the operation, I was constantly saying 'I have a headache, I have a headache' and I suffered a lot afterwards. Painkillers were not sufficient"*) and lasting to date (*"I used to suffer from migraine twice a year, and now I think I suffer from it almost once a month"*). Conversely, one patient's relative reported a current decrease in these events *("she has less headaches with the neurostimulato*r"). Temporarily experiencing severe headaches was however also mentioned by the relative of one patient from the MUMC+ cohort (*"especially the first months after that operation, she was continuously complaining about headaches and before the operation she never suffered from headaches"*).
We additionally recorded single instances of pain in the rest of the body, with an acute occurrence of shoulder pain (*"I noticed a pulling sensation in my shoulder, as if my muscle reacted to the stimulation"*) and of temporary pain in the fingers *("I had such pain in my fingers, I could hardly move my fingers"*).

Weight. Weight gain was mentioned both as a temporary (*"I gained weight at first, ...and then that went down again after a strict diet")* and current occurrence, from patients as well as one patient's relative (*"she has gained some weight, but I think that is all medication-related, I think it is 10 to 15 kg since she has the DBS"*).

Motor functions. Physical restlessness was the most common change in motor functions, experienced by two patients for a limited period of time (*"urge to move, I couldn't lie down, I couldn't sit down, I always had to walk around, clean something up, work in the garden, when in fact I was exhausted and couldn't sleep"*), and by one patient

currently as "fluctuating" leg restlessness (*"I had restless legs before the operation, after the operation it seemed less. When they had set up the stimulation, I didn't notice it, but when they increased the parameters too quickly, I suffered a lot of restless legs again, and now it seems to be less now that we are increasing the parameters more slowly"*). Upon adjustment of stimulation parameters, a few patients reported an involuntary smile ("*when the stimulation was increased, I suddenly got a smile on my left side*") and involuntary jaw movements ("*my jaw started to pull to one side because of the stimulation*"). For one patient, involuntary jaw clenching presented as a temporary side-event, and was still present to date as involuntary movement (*"my relatives tell me that I often move my jaws while I don't notice it myself"*). We also recorded individual instances of temporarily frequent muscle cramps ("*especially when I wanted to stretch in the morning"),* current decrease in vocal tics, relaxation of face and neck muscles and reduced fingers strength (from the same patient that reported experiencing fingers pain after the operation).

Skin. We recorded single instances of itchier skin *("I had suffered from little wounds in the skin folds, under my breast, in my groin, on my bottom as well, which itched incredibly hard"*), pustules (*"since the DBS I have pustules in the oddest places, in my ear or on my legs"*) and weird feeling touching the scars of the DBS lead (*"on this scar, for example, if I feel it, put my finger on it, and then I move my eyes a bit up and down, for example, I have sometimes indicated that, then it crackles in my head"*).

Eyes. One patient from the MUMC+ cohort reported tearing eyes during adjustment of stimulation parameters, and current feelings of increased eye pressure (*"I sometimes find myself rubbing my eye and then I think 'that just feels like there is more tension on it than before'"*). The relative of another patient reported reduced vision since starting the DBS treatment.

Hair. Single instances of greasy hair (*"my hair is greasy much faster"*) and hair loss on lower legs ('*I have bald patches, hair loss on my shins*') were reported by patients from the MUMC+ cohort.

Speech. One patient reported slower speech (*"I have the feeling that my speech has changed, that I sometimes speak slower, that's for sure"*), and more often incomprehensible speech (*"if I am in a sort of compulsive loop, then I really start to speak incomprehensible things, then I can't understand it anymore. I didn't have that before the DBS to that extent"*).

Device-related. We recorded a few wire-related problems, with one patient reporting the feeling that the wire of the DBS system was too tight (*"I have the feeling that my neck is always under tension. So that when you lift your arm you are pulling up your whole abdomen"*), and another patient reporting a rupture. The same patient also experienced muscle inflammation due to mechanical irritation of the DBS system. We

additionally recorded single instances of feelings of warm skin during charging, and what was described as magnetic field-induced restlessness (*"I do notice a certain restlessness in my body now and then... that is triggered by a magnet in my iPhone. If I have that phone too close to me, it makes me terribly restless"*).

Others. We here list single occurrences that did not belong to or constitute any existing or new category. Upon adjusting stimulation parameters, we recorded cases of palpitations, dizziness and fainting. For a temporary period, some patients experienced dry mouth, palpitations, urge incontinence (*"I was incontinent for two years because of the DBS. I felt I had to urinate, and I could not hold it up"*) and intestinal dysfunction (*"I had diarrhea and abdominal cramps"*). The relative of one patient reported increased snoring since starting the DBS treatment.

4. Discussion

The current study aimed to increase our knowledge of the events and experiences that accompany DBS treatment for OCD, beyond the effects on OCD core symptoms. Through qualitative analysis methods, we categorized a wide variety of psychological and physical changes in the life of operated patients.

Among the psychological experiences associated with DBS, more than half of the patients reported either temporary or stable mood improvements. This result is not surprising, as a decrease in depressive feelings and/or symptoms is universally reported across studies in a good proportion of patients, and is generally systematically corroborated with standardized questionnaires (1, 3, 4). Whether this is a primary or secondary effect of DBS is difficult to discern, as different reasons for this decrease can be considered. First, depression is the most common comorbidity of OCD (5, 16). Considering that the VC/VS and BNST are also used as anatomical targets for DBS in the treatment of depression (17, 18), it is plausible that electrical stimulation of these brain structures may directly influence the occurrence of depressive symptoms, parallel to the effects on obsessions and compulsions. Alternatively, an improvement in OCD core symptoms could pave the way for a series of subsequent changes in affect. In this regard, it has been previously suggested that diminishing anxiety and tension may give way to increased trust and openness, so that patients become more self-confident, self-reliant and assertive, but can also feel more easily annoyed, impatient or disinhibited (7). We indeed recorded several instances of generally becoming more calm, more sensitive, experiencing different emotions more strongly, feeling more self-confident or resilient, being more talkative, more impulsive, verbally disinhibited, and having more energy. These changes may not be appropriately characterized by current standardized

questionnaires administered throughout the course of DBS treatment, but constitute an important part of life post-surgery that should be carefully monitored.

The available literature on DBS outcomes for OCD treatment describes hypomania as the most frequent psychological (adverse) effect (1). A recent clinical cohort study including 70 patients recorded the occurrence of hypomania in 39% of patients, characterized by symptoms like restlessness, agitation, impulsivity, and sleep disturbances (19). A similar study reported hypomanic transient episodes in 45% of 20 patients (20). We here recorded several instances of mental and physical restlessness, impulsivity, sudden and intense crying or laughing episodes, and sleep problems. However, because we did not cluster the different experiences into likely diagnoses, we cannot explicitly confirm whether the prevalence of hypomania would here be similar compared to previous work.

In our study, long-lasting cognitive impairments in short-term and/or long-term memory were the most consistently reported across patients from both cohorts (62%), alongside decreased concentration (37%) and word-finding problems (37%). Notably, 6 out of the 7 interviewed relatives also mentioned their occurrence. This is highly consistent with previous accounts of post-DBS subjective cognitive complaints, occurring in up to 50% of operated patients (3, 4, 11). Linking these events univocally to DBS treatment is however difficult, considering that these impairments are generally not confirmed by formal neuropsychological testing (3, 10, 11, 21), and that little is known about the factors that influence the discrepancy between objective and subjective cognitive abilities.

Physical changes were less consistent across patients, and we mostly recorded singular experiences spanning various domains. Yet, sleep disturbances occurred in 44% of patients, although primarily as transient events resolving over time, in line with what was previously reported (11). Although not addressed in the present study, switching to a regimen where the stimulator is turned off during the night might represent a solution to address this issue and improve how patients tolerate DBS. It remains to be determined whether the efficacy on OCD core symptoms is however maintained under this regimen. Reports of severe headaches were specific to BNST patients, affecting 3 out of 5 patients. Despite previous accounts of surgery/device-related headaches in at least 15% of patients following DBS in the neighboring anterior limb of internal capsule (11), we did not record the same in our cohort of VC/VS patients. Finally, congruously with a few previous reports (22, 23), 25% of patients reported perceived changes in body temperature, manifesting as excessive sweating or feeling of a warm glow during adjustment of stimulation parameters.

Beyond any valuable attempt at tracing consistent patterns in the data, the attention and space given to individual experiences is the strength of in-depth, qualitative

studies. Notably, for the psychological and physical experiences here discussed as the most frequently occurring, we recorded instances of change going in the opposite direction, with reports of e.g., increased concentration, worsening in mood, flattened emotions, increased anxiety or improvements in sleep setting against their counterparts. Knowledge about this variability is fundamental to appropriately inform patients about the ways DBS can impact different aspects of their lives, thus fostering their involvement in the decision-making process (24), while acknowledging that every experience is to some extent different from another. In addition, acquiring complete knowledge of all possible accompanying events of DBS treatment can help develop comprehensive assessment and monitoring tools to integrate routine clinical follow-ups and, importantly, increase patients' support. Patients might indeed find difficult to manage the new feelings, behaviors and occurrences that characterize their life during DBS. For example, long-term follow-up studies have shown that patients' quality of life improved in all but the social domain (11, 25). It is possible that having to deal with these changes without the appropriate tools might render (re-)integration in the social world more difficult. It thus stresses the importance of including psychotherapy within the whole DBS treatment package to help patients navigate their new self (7, 26).

The use of semi-structured interviews allows complete openness to the patient's experience and priorities, without constricting patients' reports to pre-determined scales or categories. Characterizing the experience of 16 patients within this context thus ensures a level of depth and wealth of information that comparable quantitative studies would lack. Interviewing the patients' relatives then adds a valuable dimension to the research, enabling referral and tracing of experiences or events that might not be recognized or reported by the patients themselves. Nonetheless, several limitations need to be considered when interpreting the results. First, all reported experiences must be framed accounting for the risk of recollection bias, especially for transient events not present at the time of the interview. Particularly, the interpretation of the results as acute, temporary or current occurrences urges caution, as the duration of DBS treatment varied considerably across our patients, ranging from a minimum of five weeks to a maximum of 10 years. It is thus possible that experiences reported by the patients in the first period after surgery, now classified as current, could possibly be only transient when considered in the longer run. We thus stress the importance for future studies to qualitatively follow the longitudinal development of these, and potentially others, experiences throughout the course of DBS treatment. Furthermore, we coded and reported what patients and their relatives discussed, without attempting any clustering based on whether these experiences could be directly or indirectly, likely or unlikely related to DBS. We acknowledge that several factors might additionally contribute to the reported experiences, for example patients' comorbidities, their expectations, or changes in

medication throughout the course of DBS treatment. In addition, we recorded subjective experiences as mentioned by patients and their relatives, but we did not address their severity regarding nuisance or the limitations that such experiences imply. Because we employed interview methods centered around patients spontaneous reporting, we can however hypothesize that the categorized occurrences represent those with a bigger remark in the life of the patients. Nonetheless, future studies should aim to assess the impact of such experiences, by correlating them with patient's clinical history and indices of e.g., quality of life or level of functioning. Finally, we here recorded experiences from two independent cohorts of patients, with electrodes implanted in the VC/VS and the BNST. This has the advantage of increasing the representativeness of our sample, allowing to categorize the experiences of diverse patients, operated in different centers and in different anatomical locations. In principle, this approach is valuable to understand similarities and differences in the effects of electrically stimulating different brain structures. However, the small size of the BNST sample, the between-group difference in the duration of DBS treatment and the anatomical proximity between BNST and VC/VS, do not allow any definitive conclusion to be made yet about differences and similarities between anatomical locations. Additionally, recruitment for the present study was not continued until reaching full saturation of the data. We thus encourage future studies to employ both qualitative and quantitative approaches to potentially expand the set of currently reported experiences, and quantify their prevalence across patients operated in different anatomical locations.

5. Conclusions

This study expands our knowledge of DBS-related experiences during treatment for OCD, showing similar results to what has been reported in the literature, while adding a valuable dimension with the inclusion of the patients' and their relatives' very own perspective. Both homogeneous and heterogeneous patterns were identified across patients, and both are deemed necessary to fully understand DBS effects. We focused on experiences beyond specific improvements in OCD core symptoms, and we confirmed that DBS impacts many aspects of the patients' life, how they see themselves, feel and behave. This knowledge can first of all improve shared decision making between patients and treating psychiatrists/neurosurgeons before DBS (24). Additionally, results from this study contribute to developing standardized, comprehensive assessment tools to be used systematically across centers for longitudinal monitoring of DBS-related events and experiences throughout the course of treatment.

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Supplementary Material

Table S1. Topic-list. Three main topics were covered during the interviews (i.e., OCD, DBS procedure and DBS effects). The table reports more specific questions that could be asked, flexibly depending on what was mentioned by the participants.

OCD
- Can you tell something about yourself? When did your OCD start? - How bad did you suffer from OCD? - Which kind of therapies did you undergo?
DBS PROCEDURE
- When was the first time you have heard of deep brain stimulation? - When did you decide to undergo surgery? - When did you undergo surgery? - Were you well-informed about the possible complications and adverse events? - Was it necessary for you to go back to the physician a few times to adapt the stimulation settings? - Do you have the same settings for a while now?
DBS EFFECTS
- What were the effects on your OCD symptoms? - Except for the changes in terms of OCD symptoms, have you noticed any other effects? o Do you think this is caused by the stimulation? o Have you noticed any mental or physical effects? o Did you experience these effects as positive or negative? o Were these effects somehow expected or unexpected to you? o How often do you experience or used to experience these effects? o What kind of activities trigger these effects? When do you experience them?

CHAPTER 7

INDIVIDUALIZED, CONNECTOME-BASED, NON-INVASIVE STIMULATION OF OBSESSIVE-COMPULSIVE DISORDER DEEP-BRAIN TARGETS: A PROOF-OF-CONCEPT STUDY

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NeuroImage. Under Review

Abstract

Treatment-resistant obsessive-compulsive disorder (OCD) generally improves with deep-brain stimulation (DBS), modulating pathological neural activity of implantation site and connected brain-wide networks. However, its invasiveness, side-effects and lack of customization, make non-invasive treatments preferable. Harnessing the well-evidenced network effects of cortical transcranial magnetic stimulation (TMS), connectivity-based approaches have emerged for depression that aim at influencing remote regions connected to the stimulation site. We here investigated whether the networks of effective OCD DBS targets (here subthalamic nucleus [STN] and nucleus accumbens [NAc]) could be modulated non-invasively with TMS. In a proof-of-concept study with nine healthy individuals, we used 7T magnetic resonance imaging (MRI) and probabilistic tractography to reconstruct the fiber tracts traversing manually segmented STN/NAc. Two TMS targets were individually selected: the cortical region mostly connected to the right STN and that mostly connected to both right STN and NAc. In a sham-controlled, within-subject cross-over design, TMS was administered over the personalized targets, located around the precentral and middle frontal gyrus, respectively. Resting-state functional 3T MRI was acquired before, and at 5 and 25 minutes after stimulation to investigate TMS-induced changes in the functional connectivity of the STN and NAc with other regions of the brain. Static and dynamic seed-to-voxel correlation analyses were conducted. TMS over both targets was able to modulate functional connectivity of both STN and NAc, engaging both overlapping and distinct networks, and unfolding following different temporal dynamics. Given the relevance of the engaged networks to OCD pathology, we argue that a personalized, connectivity-based procedure is worth investigating and pondering further as potential last-resort treatment for refractory OCD.

1. Introduction

Obsessive-compulsive disorder (OCD) is a severe neuropsychiatric condition, ranked among the most common (1) and most debilitating (2, 3) psychiatric disorders. Despite exhaustive use of psychotherapy and pharmacotherapy, an estimated 10-20% of OCD patients still suffer from severe refractory symptoms (4). In the last decades, deep brain stimulation (DBS) has surfaced as promising last-resort option for treatment-resistant patients, offering significant improvement to their clinical symptoms, general level of functioning and quality of life (5-9). By stereotactic electrodes placement at specific locations in the brain, the discharge of constant or intermittent high-frequency electrical pulses modulates pathological neural activity (10, 11). Both white matter tracts (e.g., anterior limb of the internal capsule [ALIC], inferior thalamic peduncle, median forebrain bundle) and gray matter structures (e.g., nucleus accumbens [NAc], subthalamic nucleus [STN], bed nucleus of the stria terminalis) have been targeted (8, 12-16) in OCD patients and resulted in comparable response rates (~47% symptom reduction in 50-60% of patients) (6, 17). Although the exact mechanisms of action remain elusive, the distal effects of this highly focal stimulation on brain-wide networks are acknowledged (18, 19), and have prompted the idea that a common neuronal circuit might mediate the observed clinical improvement. The last years have thus seen a rise in the number of connectomic studies, looking at how different DBS targets promote clinical efficacy via connected networks (20). The largest study thus far to investigate the tractographic profile associated with successful DBS included a total of 50 patients from four independent cohorts, targeting the NAc or the STN (21). The results suggest that electrical modulation of a central subsection of the ALIC, connecting the lateral and medial prefrontal cortex with the thalamus and the STN, might be key to relieving obsessions and compulsions. Congruent findings have followed from two independent research groups (22, 23), and overall convincingly ascribe to connectivity patterns of DBS target sites a pivotal role in promoting good clinical outcome.

Notwithstanding its benefits, the risks inherently associated with an invasive surgical procedure, the rare yet existent reported side-effects (9, 24), and the still limited knowledge on individual target selection and indicators of clinical response (25), impede wider applications of DBS (26). Within this context, it is thus desirable to perfect less invasive treatment options. Transcranial magnetic stimulation (TMS) is by now an established, valuable alternative in the treatment of depression (27, 28), and great effort has been devoted to researching its value for other psychiatric disorders (29). In OCD, several combinations of stimulation targets (e.g., bilateral or unilateral dorsolateral prefrontal cortex, supplementary/pre-supplementary motor area, orbitofrontal cortex) and protocols (high frequency, low frequency) have been investigated using standard

TMS coils (30-32). Using trains of magnetic pulses, TMS induces electric currents and action potentials in underlying superficial cortical layers, up to an approximately appreciated 3cm depth (33, 34). Despite positive results, there is currently no evidenced superiority of one specific target/protocol combination, and the decision on where to stimulate is still to some extent experimental. The use of deep TMS coils, specifically built to reach slightly deeper areas (~3-5cm below the skull), is on the other hand now standardly applied, with a high-frequency TMS protocol stimulating the dorsal anterior cingulate cortex having received FDA clearance for the treatment of refractory OCD in 2019 (35, 36). However, the lack of replication across wider cohorts and tailoring on individual patients is still recognized as a general shortcoming, stimulating further research into alternative approaches.

As with DBS mechanisms of action, TMS effects are also known to affect the networks of regions connected to the stimulation site and not to be restricted therein (37-41). In keeping with a mechanistic understanding increasingly relying on networks rather than regions, the fields of invasive and non-invasive brain stimulation have started to converge and inform each other's experiences. Particularly in the context of depression, a number of connectivity-based TMS approaches have emerged, where (frontal) stimulation targets are chosen based on functional (42-44) or structural (41) connectivity to deeper structures (subgenual cingulate) key to the disorder pathology and to DBS treatment. Harnessing the evidenced network effects of cortical TMS, such connectivity-based approaches might increase the likelihood of effectively influencing subcortical structures with a key impact on clinical symptoms. Given the accumulating evidence in the context of depression (45), the scope of such approach may conceivably widen to other psychiatric disorders.

In the current proof-of-concept study, we propose a personalized, connectivity-based TMS procedure that is informed by the experience of DBS for OCD treatment, which overall highlights the key role of connectivity patterns of stimulation sites in relieving symptoms. Specifically, in a sample of healthy volunteers, we investigate the feasibility and effect of a paradigm for TMS targeting that relies on individual structural connectivity to known OCD DBS targets. Although overall no superior stimulation site has been identified for DBS, we focus on those for which a connectomic model has been validated (21, 22, 23): the STN and the NAc. In each individual, using high resolution 7 Tesla magnetic resonance imaging (MRI) data and advanced methods for probabilistic tractography, we identify two accessible cortical stimulation sites displaying the strongest connectivity to either one or both nuclei. Using a TMS-functional MRI setup, we address the question whether and how the networks of these deep-brain nuclei can be modulated non-invasively, as measured by changes in their functional connectivity

(FC) with other regions of the brain. We finally discuss TMS-induced FC changes across the identified stimulated sites in light of their potential relevance for OCD treatment.

2. Materials and Methods

2.1. Participants

Nine healthy, right-handed volunteers took part in the current study (age 18-25, 3 females), after one participant dropped out. Participants were screened for TMS and MRI contraindications, and excluded accordingly when necessary. The experiment was approved by the Ethics Review Committee Psychology and Neuroscience (ERCPN) of Maastricht University, and all participants provided written informed consent. At the end of the experiment, participants filled a questionnaire about their experience, asking to rate on a scale from 0 (not at all) to 100 (extremely) comfort and tolerability of stimulation across conditions.

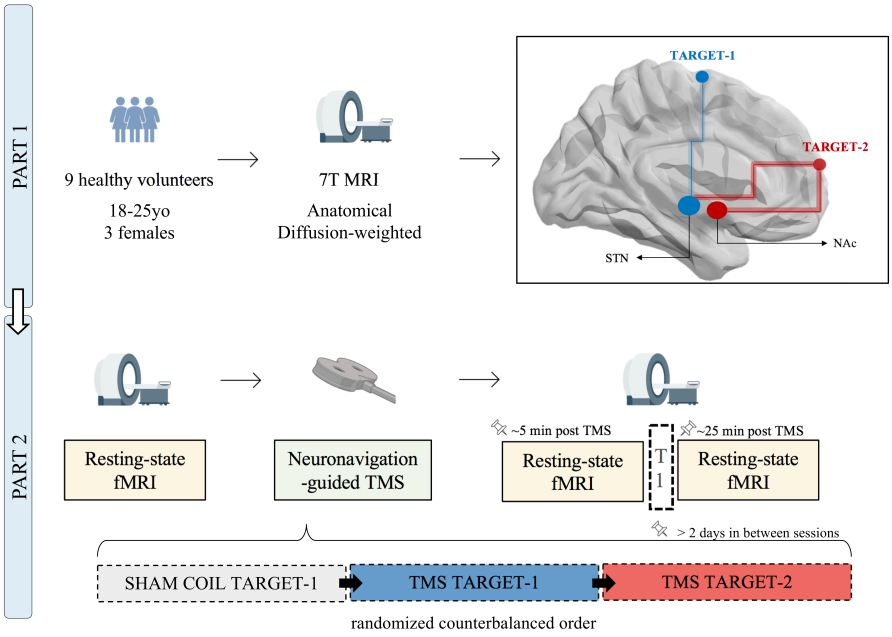

Figure 1. Schematic representation of study design. First, participants underwent 7T MRI scanning, acquiring anatomical and diffusion-weighted imaging data. In each individual brain, we used probabilistic tractography to reconstruct fiber tracts traversing manually segmented STN/NAc and reaching the cortex. The cortical region mostly connected to the STN (target-1) and that mostly connected to both STN and NAc (target-2) were selected as TMS targets (*PART 1*). In a within-subject cross-over design with separate sessions, continuous theta burst stimulation was administered over the two individually-defined targets. Additionally, a sham coil over target-1 was used as control condition. The order was randomized and counterbalanced across participants. A 10-minute resting-state fMRI protocol was acquired before and at two time points after stimulation, interleaved by an anatomy scan (*PART 2*). yo: years old; MRI: magnetic resonance imaging; STN: subthalamic nucleus; NAc: nucleus accumbens; fMRI: functional MRI; TMS: transcranial magnetic stimulation; T1: T1w anatomical scan.

2.2. Procedure

A schematic representation of the study procedure is shown in **Figure 1**. First, participants were scanned on a 7 Tesla MRI scanner, where high-resolution anatomical and diffusion-weighted imaging (DWI) protocols were acquired. In each individual brain, the anatomical data was used to manually segment bilateral STN and NAc. DWI data was preprocessed and probabilistic tractography was used to reconstruct the fiber tracts seeded from and traversing each segmented deep brain structure and reaching the cortex. For each participant, we selected two cortical regions as targets for the subsequent TMS procedure: the cortical region mostly connected to the STN (target-1), and the cortical region mostly connected to both STN and NAc (target-2). In a within-subject, single-blind, cross-over design with separate sessions on different days, we administered TMS over the two individually-defined cortical targets. Additionally, placebo stimulation using a sham coil over target-1 was used as control condition. The order was randomized and counterbalanced across participants. During each session, participants were first scanned on a 3 Tesla MRI scanner to acquire baseline anatomical and resting-state functional MRI (rs-fMRI) protocols. Once outside the scanner, we used neuronavigation to correctly place the TMS coil over the stimulation target, and applied continuous theta-burst stimulation (cTBS). Within five minutes from end of stimulation, participants underwent a second MRI scan to acquire two follow-up rs-fMRI protocols, interleaved by an anatomy scan.

2.3. MRI protocols

For the first part of the study, we acquired T1, T2 and DWI data on a 7T Siemens Magnetom MRI scanner (Siemens Medical Solutions, Erlangen, Germany) using a single-transmit 32 channel head coil (Nova Medical) at Scannexus (Maastricht, the Netherlands). The T1w scan was acquired using a magnetization prepared 2 rapid acquisition gradient echoes (MP2RAGE) sequence covering the whole brain with 0.7mm isotropic voxel size (repetition time (TR)=6000ms; time to inversion $(TI)_{(1,2)}$=[800ms,2700ms]; time echo (TE)=2.47ms; flip angle $(FA)_{(1,2)}$=[4°,5°]; generalized autocalibrating partially parallel acquisition (GRAPPA)=3; matrix size=320x320; 224 slices). The T2w scan was acquired using a multiecho gradient recalled echo (GRE) ASPIRE sequence covering the subthalamic nucleus with 0.5 mm isotropic voxel size (TR=34ms; $TE_{(1,2,3,4)}$=[2.66ms,7.35ms,14.7ms,22.1ms]; FA=12°; GRAPPA=2; matrix size=336x448; 96 slices). When acquiring these anatomical images, dielectric pads were used to improve transmit efficiency in temporal areas (46). DWI scans were obtained using a multi-band diffusion-weighted echo-planar imaging (EPI) protocol (TR=5000ms; TE=70ms; FA=90°, GRAPPA=3; matrix size=96x96; slices= 60), acquiring multiple b-value shells at b=1000 (12 directions), 2000 (27 directions)

and 3000 s/mm^2 (53 directions), alongside 11 b=0 s/mm^2 volumes, at 2.0mm voxel resolution. Six additional b=0 s/mm^2 volumes were acquired with opposite phase-encoding direction.

For the second part of the study, anatomical and rs-fMRI data were acquired on a 3T Magnetom Prisma Fit scanner using a 64-channel head/neck coil (Siemens Medical Solutions, Erlangen, Germany). Whole-brain T1w scans were acquired using a MPRAGE sequence with 1.0mm isotropic voxel size (TR=2300ms; TI=900ms; TE=2.98ms; FA=9°; GRAPPA=2; matrix size=256x256; 192 slices). Resting-state functional runs of 10.11 minutes (462 volumes) were collected using a multi-band EPI sequence (TR=1300ms; TE=32.60ms; FA=70°; multi-band acceleration factor=4; matrix size=104x104; 60 slices). Five additional volumes were acquired with opposite phase-encoding direction.

2.4. Manual segmentation of subcortical nuclei

Bilateral STN and NAc were manually segmented in individual space using Insight Toolkit (ITK-SNAP, v3.4.0 www.itksnap.org). The anatomical landmarks used to identify the boundaries of the structures were based on previous literature (47-50). Based on the T1w UNIFORM image, the NAc was located anterior to the posterior border of the anterior commissure, lateral to the inferior border of the lateral ventricle, ventral to the caudate nucleus and internal capsule, and dorsal to the external capsule and Broca's diagonal band, appearing in a round, biconvex, dorsally flattened shape (47, 49).

A Quantitative Susceptibility Mapping (QSM) image was reconstructed from the multi-echo T2w image to obtain better contrast for STN delineation, using the Sepia toolbox (51) within Matlab (Matlab R2019b; Mathworks Inc). The STN was identified medial to the ventral area of the globus pallidus, lateral and anterior to the red nucleus, and dorsomedial to the anterior edge of the substantia nigra, appearing in an oblique position in all three planes (48, 50). The size of the NAc and STN has been variably reported in the range of 300 to 800mm^3 (52-54) and approximately 100mm^3 (48, 55), respectively. Individual volumes and average sizes were calculated across participants. All segmentations were visually inspected by an experienced stereotactic neurosurgeon.

2.5. DWI preprocessing, probabilistic tractography and TMS target selection

DWI data preprocessing and probabilistic tractography were performed using MRtrix (v3.0.2, http://www.mrtrix.org/). Preprocessing included denoising, Gibbs ringing artefacts removal, eddy-current, motion and EPI-induced distortions and bias field correction. Following unsupervised estimation of response functions for white matter, grey matter (GM), and cerebrospinal fluid (CSF) (56), multi-shell multi-tissue

constrained spherical deconvolution was used to decompose the diffusion MR signal in WM fiber orientation distributions (FODs), and GM and CSF compartments (57-59).

We performed whole-brain tractography with second-order integration over FODs probabilistic algorithm (60) to reconstruct a tractogram of 10 million streamlines, using dynamic seeding (61) in 0.7 step size, and imposing a maximum track length of 250mm. We additionally performed unidirectional targeted tractography, seeding at random within the bilateral STN and NAc, keeping all parameters at default or same as in whole-brain tractography. To improve the biological accuracy of the reconstructions, for both whole-brain and targeted approaches we employed anatomically-constrained tractography, using tissue priors to inform biologically realistic streamlines generation and ending (62). To allow quantitative inferences on the reconstructed streamlines, spherical-deconvolution informed filtering of tractograms (SIFT2) was used on the combined whole-brain and targeted tracking data to proportionally match the streamline density to the estimated density of each fiber population in every voxel of the image (61).

The sum of streamline weights obtained from this step was then quantified in a connectome matrix (63), using 210 cortical and 34 subcortical regions from the Brainnetome Atlas (64), alongside the manually segmented bilateral STN and NAc. All regions were coregistered to native DWI space as follow. The T1w image was registered to the MNI152 1mm template using Advanced Normalization Tools (ANTs v3.0, http://stnava.github.io/ANTs/) *SyN* registration (65), then applying the inverse of the warp fields and generic affine matrix to the parcellation image. The T1w image was coregistered to the T2w image using ANT's registration tools with specific parameters for partial slab registration (https://github.com/ntustison/PartialSlabEpiT1ImageRegistration), and the inverse transform was then applied to the STN segmented volumes. A two-step rigid body registration was finally used to align the T1w image to the DWI image using the FMRIB Software Library (FSL v6.0; http://www.fmrib.ox.ac.uk/fsl) boundary-based registration (66), and the inverse of the rigid transform was applied to all T1 space parcel images.

Based on the individual connectivity matrix, two regions were selected: the cortical region displaying the strongest connectivity (i.e., highest streamline weights) with the STN (target-1), and the cortical region displaying the strongest connectivity (i.e., highest summed streamline weights among the nodes in the 80th percentile of the connectivity distribution of both nuclei) with the STN *and* NAc (target-2). Both right and left nuclei were considered, and the hemisphere displaying the strongest connectivity was chosen per individual. We extracted from the combined tracking data all tracks traversing the STN and NAc, we mapped the streamline endpoints to an image

(67), and we selected as individual stimulation target the highest-intensity voxel within the previously identified most-connected cortical region. To aid visualization and TMS targeting, the final mask was dilated by 3 voxels.

2.6. TMS protocol

TMS was delivered using a figure-of-eight coil (MCB70) connected to a X100 MagVenture stimulator (MagVenture, Farum, Denmark). For precise coil placement and stimulation, neuronavigation was performed using Localite TMS Navigator software (LOCALITE Biomedical Visualization Systems GmbH, Sankt Augustin, Germany). When possible, the entry point automatically calculated at the shortest distance from the target was chosen. In case the entry point would fall on unreachable locations (e.g., the TMS coil would cover the participant's eye), or raise discomfort and safety concerns, we calculated different entry points at a largest distance from the target, and moved the coil upward to either option until an acceptably comfortable position was reached. We used a cTBS protocol, delivering 50Hz triplets of pulses 5 times a second for 40s (600 pulses in total). Stimulation intensity was set at 100% resting motor threshold, determined by finding the right motor cortex and adjusting stimulation intensity until observing a visible movement in the contralateral finger in half of the trials (68). A purpose-built placebo TMS coil (MC-P-B70, MagVenture, Farum, Denmark) with strong attenuation of the magnetic field was placed over target-1 as control condition. During the stimulations, the coil was held tangentially to the scalp with a handle orientation at a 45-degree angle to the midline.

2.7. Rs-fMRI preprocessing and functional connectivity analysis

Rs-fMRI preprocessing was performed following the minimal processing pipelines for the Human Connectome Project, described in (69). Briefly, anatomical images were minimally preprocessed (bias field correction), segmented (using Freesurfer v5.2, https://surfer.nmr.mgh.harvard.edu/) and registered to standard space, producing GM and WM masks necessary for functional preprocessing. This included motion and EPI-induced distortions correction, bias field correction, intensity normalization and registration to the T1w and MNI volume spaces, all applied in a single resampling step. FSL's independent component analysis (ICA)-based Xnoiseifer (70, 71) was then used to regress out motion timeseries and artifact ICA components. Preprocessing and analysis of the fMRI data was completed using the CONN toolbox (72 2021) within Matlab. Potential outlier scans were detected based on framewise displacement above 0.9mm. We applied spatial convolution with a Gaussian kernel at 6mm full width half maximum (FWHM). Potential confounding effects were regressed out of the data, removing noise components from WM and CSF (73), estimated subject-motion

parameters (74) and the identified outlier scans (75). Temporal frequencies below 0.01Hz or above 0.1Hz were removed from the signal.

In our first-level analyses, we computed the following voxel-level measures within the STN and NAc: amplitude of low frequency fluctuations (ALFF), estimating the variability of BOLD signal power within the defined frequency band (76), and local correlation (LCOR) maps, estimating voxel-level local coherence as the strength and sign of connectivity between a voxel and its local neighborhoods (77), defined using a 4mm FWHM Gaussian kernel. We then computed seed-based connectivity maps as the Fisher-transformed bivariate correlation coefficients between the right STN/NAc timeseries and each individual voxel's timeseries. To investigate the temporal dynamics of resting-state FC changes, we decomposed the time-course signal in sliding windows of 100s (shifted in steps of 10s) to compute the dynamic variability in seed-based connectivity. For all mentioned FC analyses, the manually segmented masks of the STN and NAc were used as seeds, limitedly to the hemisphere displaying the strongest connectivity as identified in section 2.5. General linear models were used to investigate whether a difference in FC values from pre- to post- stimulation (at 5 and 25 minutes) would differ in the active vs. sham conditions. Statistical maps were thresholded using parametric cluster-based inferences (voxel p-uncorrected < .05, cluster p-FDR< .01). Individual FC values were extracted to investigate the direction of FC changes across conditions, and planned contrasts with paired sample t-test were performed to check for a significant increase or decrease in FC in the sham and TMS conditions separately. Finally, we calculated Pearson correlation coefficients between individual difference values in FC pre- and post- TMS, and the recorded distance between stimulation target and actual coil placement, in order to evaluate the potential impact of increased distance entry-target on observed effects.

3. Results

3.1. TMS target selection and procedure

Manually segmented nuclei had an average size largely consistent with what previously reported (48, 52-55), of 99.9(±9.5) mm^3 for the right STN, 102(±11.2) mm^3 for the left STN, 420.2(±55.3) mm^3 for the right and 466(±71.9) mm^3 for the left NAc. For all our participants, the fiber tracking and target selection procedure yielded two stimulation targets located in the right hemisphere, connected to the right STN and right NAc. Accordingly, subsequent analyses were conducted limitedly to the right STN and NAc as seeds of interest. Individual MNI millimeter coordinates and atlas label of target-1 and target-2 are reported in **Table 1** and displayed in **Figure 2**. Target-1 was mostly located in the precentral and postcentral gyrus, although three participants showed STN

strongest connectivity to the superior frontal gyrus. Given the relative ease of reach, all participants received stimulation at the shortest possible distance from the target, as optimally computed by the neuronavigation software (Mean(±SD): 19.7mm (±2.68), **Table 1**). Target-2 was located in the middle frontal gyrus for all participants except one (in the orbital gyrus). Stimulation of target-2 at the shortest calculated distance was unfeasible, with the participant's eye being partially or fully covered by the TMS coil. We therefore moved the coil upward to the differently calculated entry points until an acceptably comfortable position was reached. For stimulation of target-2, we consequently registered a higher average and inter-subject variability distance entry-to-target (Mean(±SD): 33.6mm(±9.41), **Table 1**). When asked about their experience across the different sessions, all participants indicated target-2 stimulation as the most uncomfortable/unpleasant, rating the comfort with an average score of 28.75 (±18.2), and the tolerability with an average score of 37.5(±18.8).

Table1. Individual stimulation targets.

	TARGET-1			**TARGET-2**		
	MNI coordinates (mm)	Atlas label	Distance entry-target (mm)	MNI coordinates (mm)	Atlas label	Distance entry-target (mm)
Sub001	16 -25 +76	PrG, A4t	16.03	23 +57 -15	MFG, A10l	39.03
Sub002	25 +6 +66	SFG, A6dl	22.25	30 +60 -12	OrG,A12/47l	35.20
Sub003	14 -35 +78	PoG, A1/2/3tru	19.05	16 +58 -15	MFG, A10l	42.64
Sub004	19 +6 +70	SFG, A6dl	17.49	33 +66 -1	MFG, A10l	15.06
Sub005	20 -19 +78	PrG, A4t	17.47	23 +62 -12	MFG, A10l	32.83
Sub006	19 -18 +77	PrG, A4t	15.52	20 +58 -16	MFG, A10l	43.51
Sub007	16 -30 +75	PoG, A1/2/3tru	20.58	16 +58 -18	MFG, A10l	34.69
Sub008	23 -26 +74	PrG, A4t	21.89	28 +60 -10	MFG, A10l	24.30
Sub009	06 +29 +62	SFG, A8m	22.28	23 +58 -14	MFG, A10l	32.30

From left to right, we report the MNI millimiter coordinates of target-1 and target-2 stimulation, the corresponding label from the Brainnetome Atlas, and the recorded distance in millimeter between the identified target and the entry point (i.e. coil position). PrG: precentral gyrus; SFG: superior frontal gyrus; PoG: postcentral gyrus; MFG: middle frontal gyrus; OrG: orbital gyrus; t/tru: trunk region; dl: dorsolateral area; m: medial area; l: lateral area.

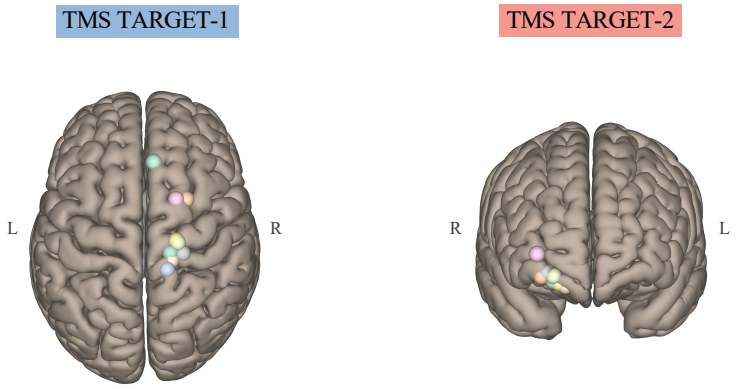

Figure 2. Individual TMS stimulation targets, defined as the (voxel) connectivity hotspot within the cortical region most connected to the STN (target-1) and that most connected to both STN and NAc (target-2). For all participants, the right hemisphere displayed the strongest connectivity patterns. L: left; R: right; TMS: transcranial magnetic stimulation.

3.2. Modulating STN functional connectivity

We did not find a significant difference in the ALFF and LCOR of the right STN following stimulation of target-1 nor target-2 as compared to sham. Hereafter, we report all clusters that significantly differed (with a p-FDR<.001) in the observed FC change (from pre- to post-) across conditions (sham vs. active stimulation). We report the direction of FC change (increase vs. decrease) and associated p-value from planned contrast testing, and we explicitly mention when the TMS-induced FC change was smaller than what observed in the sham condition.

Target-1. Stimulation of the cortical region individually most connected to the right STN (target-1) significantly increased FC between the right STN and a cluster in the left planum temporale at 5 minutes post-stimulation (k=1491; $peak_{(x,y,z)}$=[-64,-20,+12]; T=6.39; p<.001). At 25 minutes post-stimulation, we found a significant decrease in connectivity with a cluster in the right lingual gyrus (k=1533; [-16,-80,-12]; T=-6.15; p=.004), although smaller compared to the observed difference in the sham condition, and an increase in the right precentral gyrus (k=1405; [+14,-48,+76]; T=5.68; p<.001) (**Figure 3**). Variability of FC measures was computed across overlapping sliding windows to characterize dynamic changes within each 10-minute rs-fMRI protocol. We found increased variability at 25-to-35 minutes following TMS for FC with a cluster in the left paracingulate gyrus (k=472; [+02,+34,-02]; T=7.64; p<.001) and left precentral gyrus (k=339; [+04,-28,+54]; T=8.59; p<.001). The significant increased variability observed for a cluster in the left middle frontal gyrus (k=594; [-36,+44,+16];

T=10.82; p<.001) and in the right precuneus (k=414; [-10,-52,+62]; T=8.47; p<.001) was smaller than the observed difference in the sham condition (**Figure 4**).

Target-2. Stimulation of the cortical region individually most connected to both the right STN and NAc (target-2) did not significantly modulate FC of the right STN towards the rest of the brain in the first 5-to-15 minutes post TMS, as compared to sham stimulation. At 25 minutes post stimulation, we found significant connectivity changes with a cluster in the right cuneal cortex (k=1976; [+30,-68,+10]; T=-5.56). Compared to sham, planned contrast testing revealed a smaller pre-to-post difference in FC following active stimulation, not significant by itself (p=.183) (**Figure 3**). Within this second rs-fMRI scan, we found decreased variability in FC of the right STN with a cluster in the right occipital fusiform gyrus (k=407; [+24,-86,+02]; T=-8.91; p=.002) and the medial frontal cortex (k=326; [-12,+26,-20]; T=-9.36; p=.003). We observed a significantly smaller TMS-induced change in FC temporal variability to the right lingual gyrus (k=604; [+06,-64,+04]; T=-4.93), however not significant by itself (p=.077) (**Figure 4**).

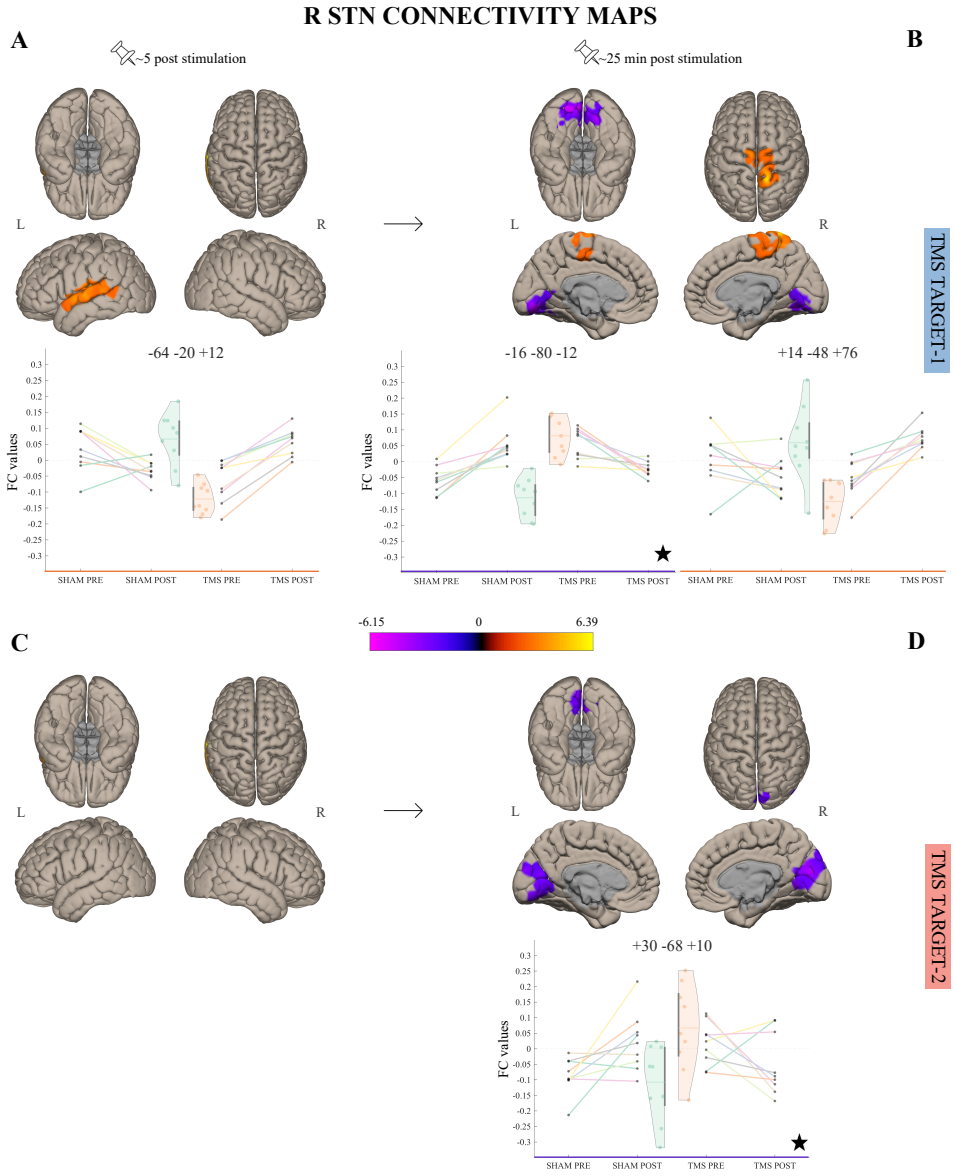

Figure 3. Connectivity maps of significant functional connectivity changes of the right STN following active as compared to sham stimulation. Significant group-level clusters from second-level general linear models are projected on a brain surface using the CONN toolbox at 5 minutes (*A, C*) and at 25 minutes (*B, D*) post target-1 (*A, B*) and target-2 (*C, D*) stimulation. Individual functional connectivity values are extracted and plotted for each significant cluster across the four contrasted conditions, represented as line-connected dots. The color of the x-axis signals the corresponding cluster on the brain surface, and peak voxel coordinates are reported. Violin plots represent the observed pre-to-post difference in the sham condition (light green) and in the active stimulation condition (salmon). We star where the TMS-induced difference was significantly smaller than the sham-induced difference. L: left; R: right; STN: subthalamic nucleus; FC: functional connectivity; TMS: transcranial magnetic stimulation.

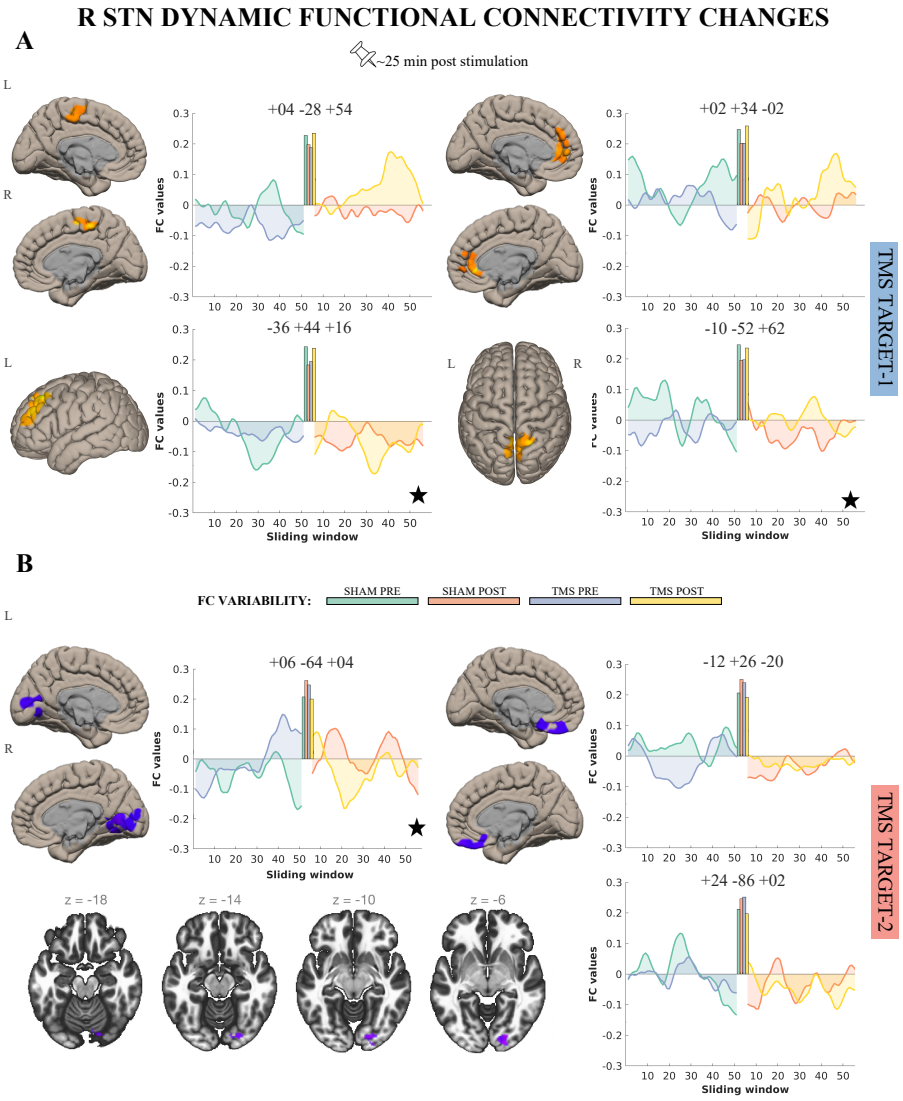

Figure 4. Dynamic connectivity maps of significant functional connectivity changes of the right STN following active as compared to sham stimulation. Significant group-level clusters from second-level general linear models are separately projected on a brain surface at 25 minutes post target-1 (*A*) and target-2 (*B*) stimulation. Peak voxel coordinates are reported. Group average functional connectivity values are extracted and plotted across time (i.e., sliding windows) for the different contrasted conditions; the left side of each graph represents the pre-stimulation condition (sham in green, active TMS in blue), whereas the right side of each graph represents the post-stimulation condition (sham in orange, active TMS in yellow). The group average temporal variability of FC across time is represented as the bar graph in the middle. We star where the TMS-induced difference was significantly smaller than the sham-induced difference. L: left; R: right; STN: subthalamic nucleus; FC: functional connectivity; TMS: transcranial magnetic stimulation.

3.3. Modulating NAc functional connectivity

No significant differences emerged for ALFF and LCOR of the right NAc following either TMS conditions as compared to sham stimulation.

Target-1. At 5 minutes following target-1 stimulation, we observed significant decreases in the FC of the right NAc with the left lateral occipital cortex (k=1773; [-38,-56,+30]; T=-5.11; p<.001), and the left frontal pole (k=1291; [-06,+46,+28]; T=-4.76; p=.005). We also observed a FC decrease with a large cluster in the left ventrolateral prefrontal cortex (k=3746; [-42,+24,-18]; T=-6.40; p<.001), although smaller than the sham difference. FC to the right lateral occipital cortex significantly increased (k=2874; [+36,-78,+28]; T=7.47, p=.001). At 25 minutes following stimulation, only FC to the cluster in the right lateral occipital cortex was still significantly increased (k=1503; [+44,-70,+30]; T=8.67; p=.008) (**Figure 5**). When looking at dynamic FC, we found significantly higher variability in FC with a cluster in the left inferior frontal gyrus pars opercularis (k=408; [-48,+12,+04]; T=5.10; p=.003) between 25 and 35 minutes following TMS (**Figure 6)**.

Target-2. At 5 minutes following target-2 stimulation, we found a significant decrease in FC with a cluster in the left frontal pole (k=1829; [-28,+18,-36]; T=-5.20; p=.01), although smaller than the observed sham difference, and an increase in the right caudate (k=1041; [-02,+06,+16]; T=8.35; p=.003). No changes significantly persist at 25 minutes post-stimulation (**Figure 5)**. When assessing dynamic FC changes within the first 5-to-15 minutes, we found a significant decrease following TMS in FC variability with a cluster in the right supramarginal gyrus (k=315; [+50,-44,+50]; T=-6.63; p=.004), and an increase in the left postcentral gyrus (k=312; [-06,-38,+68]; T=13.88; p<.001). Within 25-to-35 minutes post TMS, we found increased variability in the FC with two clusters in the precuneus (k=557; [+02,-40,+62]; T=6.69; p=.01), (k=295; [-04,-54,+08]; T=7.63; p=.12), and in the left precentral gyrus (k=413; [-38,-14,+70]; T=6.74; p<.001), all showing smaller modulations compared to what observed in the sham condition (**Figure 6).**

3.4. Correlation with distance entry-target

Pearson correlation coefficients were calculated between observed pre-post active TMS FC change and the recorded distance between stimulation target and actual coil placement. We only found a significant negative correlation for observed changes in FC between the right STN and right cuneal cortex at 25 minutes after target-2 stimulation (r=.659, p=.05), and between the right NAc and left ventrolateral prefrontal cortex at 5 minutes after target-1 stimulation (r=.779, p=.001).

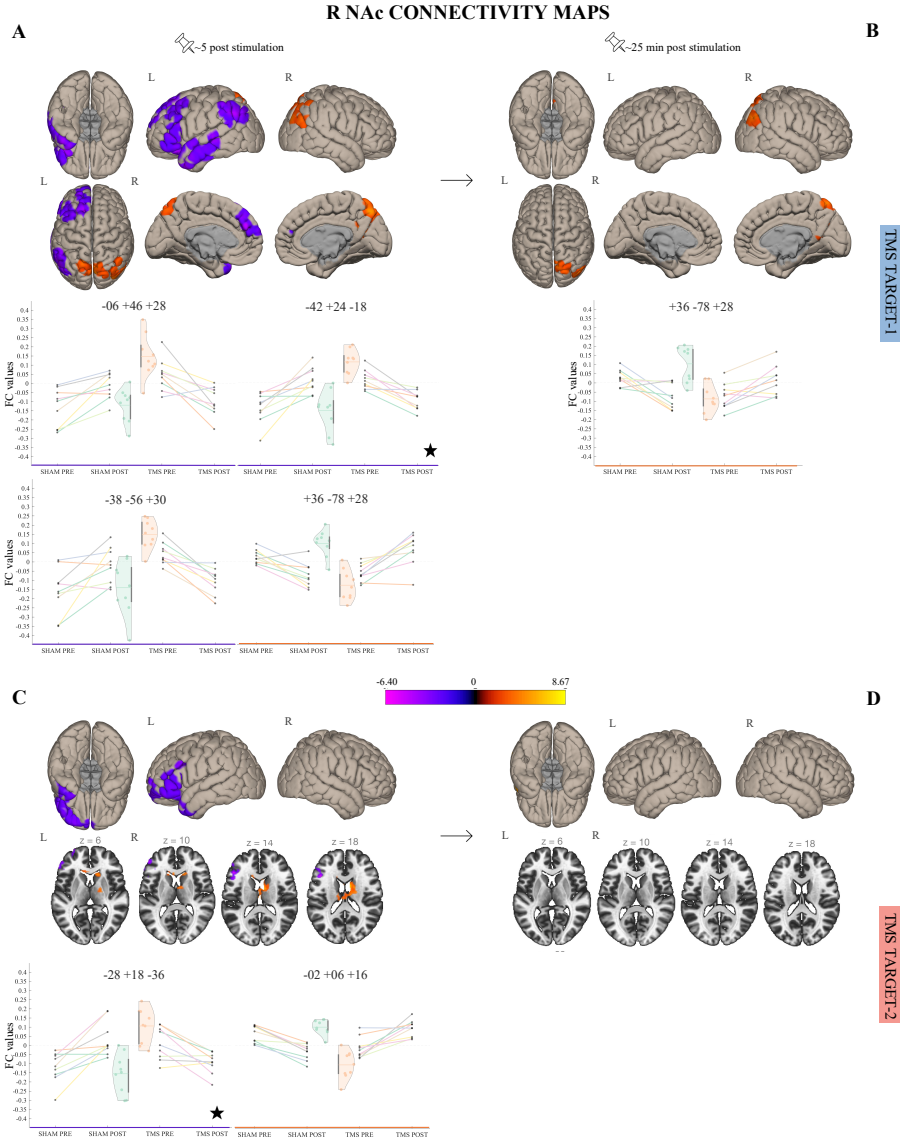

Figure 5. Right NAc connectivity maps of significant functional connectivity changes following active as compared to sham stimulation. Significant group-level clusters from second-level general linear models are projected on a brain surface at 5 minutes (*A, C*) and at 25 minutes (*B, D*) post target-1 (*A, B*) and target-2 (*C, D*) stimulation. Individual functional connectivity values are extracted and plotted for each significant cluster across the four contrasted conditions, represented as line-connected dots. The color of the x-axis signals the corresponding cluster on the brain surface, and peak voxel coordinates are reported. Violin plots represent the observed pre-to-post difference in the sham condition (light green) and in the active stimulation condition (salmon). We star where the TMS-induced difference was significantly smaller than the sham-induced difference. L: left; R: right; NAc: nucleus accumbens; FC: functional connectivity; TMS: transcranial magnetic stimulation.

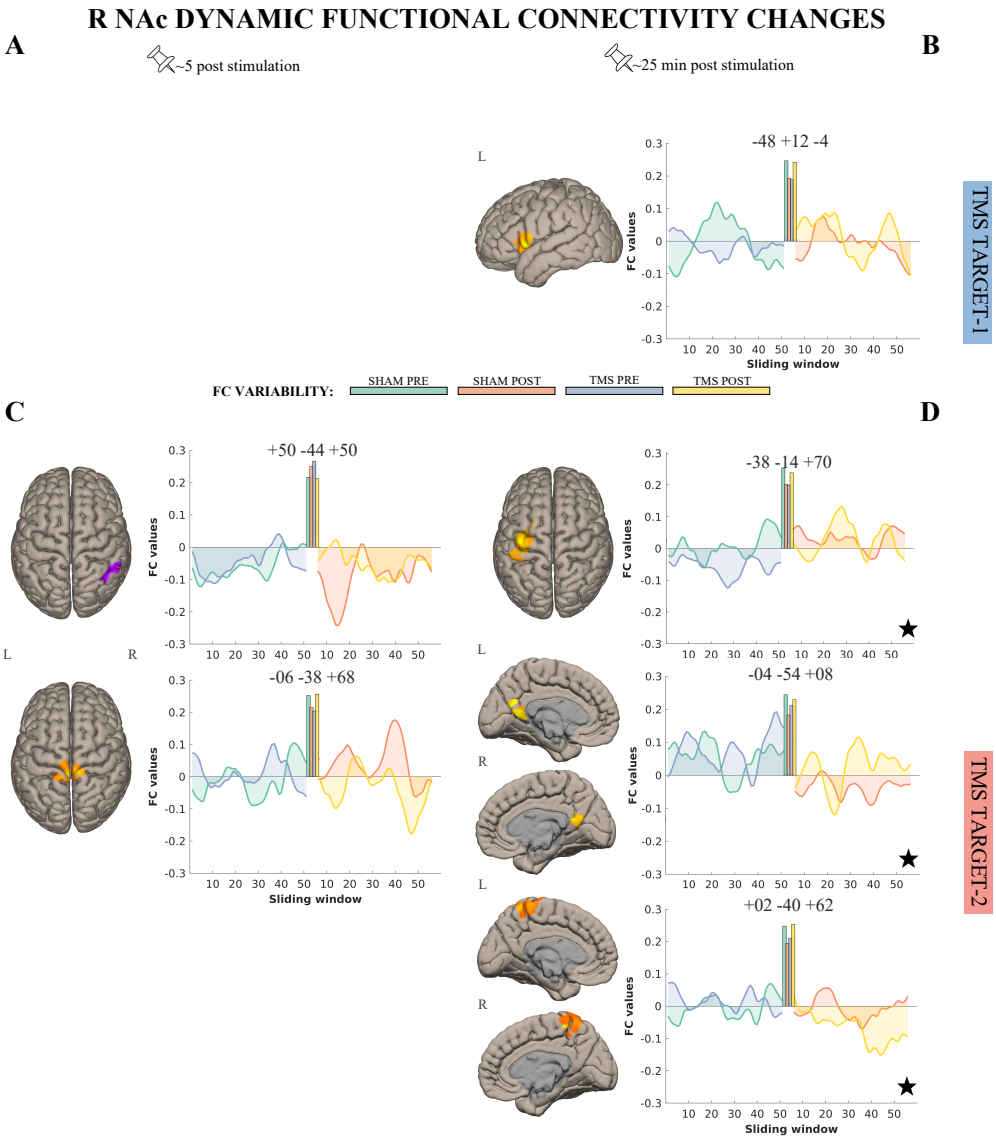

Figure 6. Dynamic connectivity maps of significant functional connectivity changes of the right NAc following active as compared to sham stimulation. Significant group-level clusters from second-level general linear models are separately projected on a brain surface at 5 minutes (*A, C*) and at 25 minutes (*B, D*) post target-1 (*A, B*) and target-2 (*C, D*) stimulation. Peak voxel coordinates are reported. Group average functional connectivity values are extracted and plotted across time (i.e., sliding windows) for the different contrasted conditions; the left side of each graph represents the pre-stimulation condition (sham in green, active TMS in blue), whereas the right side of each graph represents the post-stimulation condition (sham in orange, active TMS in yellow). The group average temporal variability of FC across time is represented as the bar graph in the middle. We star where the TMS-induced difference was significantly smaller than the sham-induced difference. L: left; R: right; NAc: nucleus accumbens; FC: functional connectivity; TMS: transcranial magnetic stimulation.

4. Discussion

The present study applied a personalized, connectivity-based procedure to TMS targeting, aiming to identify an accessible cortical stimulation target displaying the strongest connectivity to deep nuclei otherwise non-invasively out of reach. As a proof-of-concept for refractory OCD treatment, we focused on DBS targets of the known efficacy in relieving obsessive-compulsive symptoms: the STN and the NAc. Owing to the extensive body of literature proving remote effects of non-invasive brain stimulation, we hypothesized that TMS over an individually-defined cortical entry point would modulate the resting-state FC of the connected deep targets towards the rest of the brain. Our sham-controlled, offline TMS-fMRI procedure revealed both static and dynamic signatures of FC changes of both STN and NAc at two time points following stimulation.

4.1. Modulating functional connectivity networks

The STN and NAc are critical nodes of the cortico-striatal-thalamo-cortical (CSTC) loops, which decades of research convincingly linked to OCD pathology (78, 79). We will thus discuss the results in light of their potential relevance to OCD treatment, based on what is reported in the literature.

Both target-1 and target-2 were chosen based on their structural connectivity with the right STN. Consistent with our hypothesis, we observed significant changes in the FC networks of the STN, which were however detected only (for target-2 stimulation) or primarily (for target-1 stimulation) between 25-to-35 minutes following TMS. The STN primarily participates in the sensorimotor circuit, together with regions involved in the generation and control of motor behaviors and integration of sensory information, and in the ventral cognitive circuit, alongside prefrontal and thalamic regions involved in self-regulatory behaviors (80). Alterations in these networks are thought to drive dysfunctional habit formation and faulty inhibition responses, presumably explaining the persistence of maladaptive, repetitive obsessive thoughts and compulsive behaviors, despite knowledge of their irrationality and associated negative consequences (for a review, see (81)). TMS of the supplementary/pre-supplementary motor area (SMA/pre-SMA) and DBS of the STN likely act on these circuits and consequently improve the experienced symptoms. Here, stimulation of the cortical region individually most connected with the STN increased FC with a cluster of voxels in the primary motor and sensorimotor cortex, suggesting that this procedure could critically engage nodes of the sensorimotor circuit. However, despite a topographical organization is certainly present, the integration and overlap between the different CSTC loops is acknowledged (79) (81), and it is thus likely that stimulation of one circuit affects the functioning of others. For example, the STN also critically participates in the

control of emotional and motivational behaviors (82). Our results indeed show that TMS modulates the temporal variability of FC measures with a cluster in the paracingulate cortex (target-1) and ventral orbitofrontal cortex (OFC) (target-2), key components of the fronto-limbic circuit to generate, evaluate and regulate emotional responses (83), and with the medial frontal cortex (target-1), potentially influencing executive functions important for goal-directed behavior (80).

Modulation of the NAc FC network unfolded following a different temporal dynamic, with most stable changes being recorded in the first 5-to-15 minutes after stimulation. The NAc is a key component of the ventral affective circuit, together with regions involved in reward functions (OFC, ventral striatum and thalamus) (84). OCD neurobiological theories suggest that a lowered sensitivity to reward as opposed to an enhanced sensitivity to, or an aversion of, punishment might drive some avoidant behaviors (19) or feelings of anhedonia (85) that can be common in OCD patients. Studies for example report increased FC between NAc and other reward circuit regions at rest, and alterations during anticipation of reward and punishment (86), as well as poorer performance on reward-based decision-making and reward-learning tasks (87, 88), and impaired generalization of reward (but not punishment) (89). Remarkably, our results show a significant decrease in the FC of the NAc with a large cluster in the OFC. Despite only target-2 was chosen based on its connectivity with the NAc, we observed the same effect following target-1 stimulation, once again suggesting that brain stimulation is more likely to elicit a cascade of neural events rather than targeted effects only. Consistent with the knowledge that the NAc also participates to other circuitries (90), we also observed increased variability of FC measures with sensorimotor regions following target-2 stimulation. Likewise, other regions participate to the functioning of the ventral affective circuit, such as components of the fronto-limbic and ventral cognitive circuit (thus including the STN) (82). In regard to the latter, we indeed recorded both static and dynamic modulation of NAc FC with ventral cognitive components (inferior frontal gyrus and ventrolateral prefrontal cortex) following target-1 stimulation.

It should be mentioned that we here only discussed FC modulations within the different CSTC loops, but research has suggested that OCD dysfunctional circuits are not restricted therein (79), (81). Different lines of evidence have indeed suggested for example altered dynamics within and between intrinsic resting-state networks (91-94), or the special role of certain hub regions, such as the inferior parietal lobule (95), the anterior cingulate cortex (96) or the precuneus (97, 98). Our results also show modulation across visual, parietal and precuneal areas, suggesting that this procedure could also critically modulate these nodes, with potentially secondary effects on the networks in which they participate.

To conclude, we observed modulation of both overlapping and segregated functional networks following TMS at two cortical sites differently structurally connected to the STN and the NAc. It could be argued that one entry point might be more effective than another, depending on the prevalent functional and/or behavioral dysfunction of the individual patient. A neurocircuit-based taxonomy of OCD has in fact been recently suggested (81), advancing the hypothesis that patients might be clustered based on dominant dysfunction in one (or more) neurocircuit and specific phenotypic manifestations of the disorder.

4.2. Individualized, connectivity-based target definition

Connectivity-based selection procedures for TMS target definition have been established primarily in the context of depression treatment. It has been shown that subgenual-frontal FC predicts antidepressant treatment response (42, 99) and can be used to effectively identify individualized targets (43, 100, 101), with large differences on where the coil should be placed to successfully modulate deep regions (43). While most attempts at personalizing target selection relied on FC patterns, recent results suggest the potential superiority of diffusion-based targeting (41), although formal comparisons of the two approaches in patients populations are still lacking. When it comes to fiber tractography, the field is particularly aware of potential biases inherent to either deterministic or probabilistic approaches (102-104). However, improvements in the quantitative assessment of streamline reconstructions now allow more precise and reliable use of structural connectivity measures (61, 62), for example for the purpose of TMS target selection. The STN might be particularly suited to this procedure, displaying strong and widespread anatomical connectivity to the cortex (105). Non-human and human studies have distinguished three functionally different parts within the STN, differentiating by their connectivity with motor, associative or limbic areas (106, 107). The sensorimotor part constitutes as the largest, exhibiting direct connections to primary motor, premotor, SMA and somatosensory cortex, via the so-called “hyperdirect” pathway (105, 106, 108). In line with this body of literature, in the present study the cortical targets individually most connected to the STN spread across the postcentral, precentral and superior frontal gyri. Remarkably, despite the inter-individual variability in exact localization, TMS induced group-level effects on STN FC. Of note, low-frequency stimulation of the SMA/pre-SMA is ranked among the most effective TMS targets for OCD treatment, despite the inter-individual variability in clinical response remaining relatively large (32). We advance the hypothesis that another region within the sensorimotor network might lead to better results, if individually showing stronger connectivity to its subcortical components than a group target selected a priori.

In keeping with recent advances in understanding DBS mechanisms, we additionally selected the cortical region displaying the strongest connectivity to both the STN and NAc. Independent lines of evidence have indeed suggested that the closer the DBS electrode to a fiber pathway connecting the thalamus to the lateral and medial prefrontal cortex, the better the clinical response, reporting this association in different cohorts of patients targeted in either the NAc-ventral capsule or the STN (20-23). In line with what was reported, our procedure localized this region in the middle frontal gyrus, homogeneously across individuals. The OCD TMS literature counts only two studies targeting the nearby right or left OFC (109, 110), hence not allowing any conclusion to be made on efficacy in OCD patients. It should be noted that stimulation of this area comes with a number of challenges; in the present study, participants rated poorly the tolerability and comfort of this particular stimulation session, due to stimulation of facial nerves and relatively strong muscle twitches. Furthermore, placing the TMS coil at the shortest distance from target was not possible, and it thus cannot be excluded that we actually stimulated a location different than what intended. These aspects should also be critically considered when discussing the advantage of one stimulation target over another.

To conclude, our data-driven target selection approach partly aligns with what is encountered across the OCD brain stimulation literature. The idea of using neuroimaging to improve precise spatial localization and account for anatomical individual differences has long been introduced, and measurable differences on the effects of stimulation reported (111-113). It remains to be confirmed whether the large observed inter-individual variability in response to TMS for OCD can be reduced by targeting cortical stimulation sites selected based on individual structural connectivity patterns to subcortical nuclei.

4.3. Interpreting remote TMS aftereffects

Remote effects of TMS have primarily been established using interleaved TMS-fMRI paradigms, assessing the online cortical and subcortical impact of motor/sensorimotor (37, 38, 114-116), parietal (117) and prefrontal cortex stimulation (41, 118-125). Other offline studies add to this literature reporting TMS-induced modulation of widespread, connected networks (39, 40, 126-128), establishing the idea that TMS could be used to access layers lying deeper than what directly targeted at the 3cm reach of standard coils. However, understanding how these effects arise is non-trivial. When applying TMS with a running high-voltage current pulse, a magnetic field is generated that penetrates the skull and produces an electrical current sufficiently fast and strong to depolarize the underlying neural elements, elicit action potentials and trigger processes of synaptic plasticity (129). Neuronal activation at the stimulation site then transsynaptically spreads

to remote connected regions, but it is unclear whether this happens via changes in FC, or via activation-induced synaptic plasticity at the remote site itself during stimulation (130). Additionally, a number of potential confounding or covarying factors potentially play a role, and a scenario where remote effects are actually induced by e.g., unintended costimulation of non-target regions and networks is difficult to exclude (for a review and further considerations, see (130)). Of note, we considered FC changes of remote sites towards other regions of the brain, placing our outcome measure even further down the causal chain of stimulation effects, and thus further away from straightforward interpretations. Besides the problematic understanding of how these remote aftereffects arise, characterizing how they manifest is equally challenging. Distinguishing stimulation protocols based on their inhibitory vs. facilitatory effect on synaptic plasticity is admittedly oversimplified (29), even more so when considering remote effects, the direction of which is difficult to predict. Additionally, even assuming an a priori understanding of these effects, influencing the neural activity of remote regions does not imply influencing their functional connectivity in the same expected direction, as these concepts cannot be considered as a sign of one another. Our results indeed show region-specific modulations, with instances of increases or decreases in FC across different network components. Of note, in some cases we recorded smaller changes following active as compared to sham stimulation, which could be seen either as a sign that our sham procedure failed to control for secondary effects of stimulation (131, 132), or as an instance of a true inhibitory effect on the dynamic fluctuations in FC that can be normally expected (133-136).

In light of all these considerations, notwithstanding the importance of basic, combined TMS-neuroimaging studies like ours, any observed increase or decrease in the FC of (remote) networks has limited interpretability in the absence of a context where communication between these regions becomes relevant. To our knowledge, this is the first attempt at investigating targets used in brain stimulation treatment for OCD. Our proof-of-concept study established that individualized, connectivity-based TMS can modulate the functional networks of OCD-relevant deep targets. However, we underscore the importance of taking the next necessary steps, asking whether this TMS procedure elicits the same observed changes in OCD patients, and whether these changes then translate to a cognitive, emotional or behavioral shift to functional patterns. Once and if this is established, this procedure could be used as standalone treatment, or in the evaluative phase of DBS to judge which network is more easily engaged in the individual patient, and thus more likely to benefit from invasive electrode placement.

4.4. Limitations

Several limitations constrain the interpretation of our results. First, we conducted a proof-of-concept study in a small sample of healthy volunteers. Conforming to its preliminary and exploratory nature, when assessing the results we admittedly used a liberal statistical threshold that could have thus inflated the reported group effects. Replication across wider, patients cohorts is thus mandatory. Second, it is well established that the TMS-induced magnetic field decays exponentially at increasing distance from the coil (137), and that this can be compensated by adjusting stimulation intensity to the estimated scalp-cortex distance (138). This would have been particularly advisable for stimulation of target-2. However, given the low-rated comfort and tolerability, we believe that stimulating at an intensity higher than 100% resting-motor-threshold would have been unfeasible. Furthermore, we did not perform any e-field modelling to establish whether an effective stimulation intensity was achieved at the target coordinate. Thus, in keeping with considerations on remote TMS aftereffects discussed above, we cannot exclude that other factors confounding or covarying with the effects of stimulation might have influenced the observed results.

5. Conclusions

We employed a data-driven approach to identify cortical sites accessible non-invasively based on individual structural connectivity of OCD-relevant deep targets; the STN and NAc. Results from this procedure partly align with what is encountered across the OCD brain stimulation literature, yielding two cortical sites quite homogeneously distributed around the precentral and middle frontal gyrus. Our sham-controlled, offline TMS-fMRI procedure revealed both static and dynamic signatures of FC changes of both STN and NAc, with overlap and differences in the engaged networks across stimulation sites. Given the relevance of these networks to OCD pathology, we deem an individualized, connectivity-based TMS procedure worth investigating and pondering further, either as a potential standalone treatment, or in preparation to DBS, to evaluate the effects of probing the networks of deep-brain nuclei where electrodes might be subsequently implanted.

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CHAPTER 8

GENERAL DISCUSSION

In the first part of this thesis, we used different approaches to investigate psychological (**Chapter 2**), neural (**Chapter 3**) and environmental (**Chapter 4**) aspects that have been linked to obsessive-compulsive disorder (OCD), but generally span different diagnostic categories. In the second part, we first addressed a few aspects related to current uses of deep brain stimulation (DBS), systematically investigating effects on OCD symptoms that might not be due to actual stimulation of the brain (**Chapter 5**) and categorizing the full range of elicited experiences beyond changes in obsessions and compulsions (**Chapter 6**). We then suggested how the mechanisms by which neurostimulation modulates the brain can be used to guide personalized target selection for transcranial magnetic stimulation (TMS), assessing the effect of this procedure on functional brain networks (**Chapter 7**). A summary of the results of the presented studies is provided in the Appendix. In the present chapter, we discuss and integrate the findings in light of a network-based approach to understanding symptoms and brain stimulation effects, reasoning on how this knowledge can be used to guide more personalized interventions. We further highlight how the results of this thesis can be complemented by future investigations, and we remind the reader of a few methodological considerations to bear in mind when interpreting the results.

1. Network-based neuroimaging and neuromodulation

In the introduction of this thesis (Chapter 1), we outlined how the scientific approach to studying the brain moved from a localized, region-centered perspective to one considering broader circuitries. When investigating markers of psychiatric disorders, neuroimaging studies thus adapted their hypotheses and analyses strategies to the need of considering the human brain as a complex network. Connectomic and graph-theoretical approaches offer a unique tool to characterize the static and dynamic properties of brain graphs, described in terms of either functional or structural connectivity among neural elements (1). In the last decade, these methods have been widely applied across psychiatric disorders, unravelling various alterations in the organization and function of the brain connectome (2-4). Adhering to the use of this approach, the neuroimaging studies presented in this thesis substantiate these findings. In **Chapter 2**, we characterized the multimodal brain correlates of neuroticism, the single vulnerability trait most consistently associated with psychopathology, including anxiety and depressive disorders, substance use or abuse (5, 6), eating disorders (7) and, relevant to the present work, OCD (8-11). Our results show that neuroticism maps to a decrease in the voxel-wise whole-brain functional connectivity of widespread regions, spanning motor, sensorimotor and occipital areas, among others. In **Chapter 3**, we investigated OCD-related anomalies in rich-club organization, i.e., the property of

topologically central regions of the brain to establish strong and numerous connections with each other (12). Our findings of decreased rich-club organization and rich-club connectivity suggest changes in the topological arrangement of connections and their weights, with OCD patients seemingly allocating more weight to peripheral connections at the detriment of the rich-club core. Thus, the results of the present thesis feed to a solid body of research increasingly relying on network neuroscience to understand the brain basis of psychiatric disorders. Congruously with the direction that the whole field has taken, our results highlight the need to focus more on brain-wide network properties, organization and dynamics rather than mapping alterations in a few circumscribed regions defined a-priori.

The conceptual shift from regions to networks permeating neuroimaging research has also strongly impacted the neuromodulation field, influencing the understanding of brain stimulation's mechanisms and effects. Neuromodulation techniques generally deliver a stimulus (with the techniques here investigated, this is in the form of electrical currents/pulses) to alter neurological activity at a specific targeted area (13). Given their ability to act directly on the brain, these techniques can be used to treat a wide range of neurological, movement and psychiatric disorders. The observed clinical effects have been initially ascribed to the induced neuronal changes at the site where stimulation is delivered. However, studies have later started to acknowledge and investigate the effects of local stimulation on remote sites and networks, and their role in driving clinical response (14-16). The DBS literature for the treatment of refractory OCD first demonstrated that electrical stimulation of the nucleus accumbens (NAc) not only normalizes hyperactivity therein, but also acts on altered functional connectivity between the NAc and the frontal cortex (17). Since then, a wealth of connectomic studies aimed to investigate how different DBS targets promote symptoms reduction via modulation of connected networks (18-21). Results seem to converge on the idea that electrical modulation of a fiber tract connecting the lateral and medial prefrontal cortex, thalamus and subthalamic nucleus (STN), might be key to relieving obsessions and compulsions. Remote effects of TMS have primarily been established by means of concurrent TMS-magnetic resonance imaging (MRI) paradigms, assessing the online cortical and subcortical impact of motor/sensorimotor (22-26), parietal (27) and prefrontal cortex stimulation (28-36). Other offline studies add to this literature reporting TMS-induced modulation of widespread, connected networks (37-41). Contrary to the paucity in the context of OCD treatment, the depression TMS literature provides evidence linking clinical outcomes to connectivity patterns of stimulation sites, showing that antidepressant response to dorsolateral prefrontal cortex stimulation depends on its functional connectivity with the subgenual cortex (42, 43).

Thus, the fields of neuroimaging, invasive and non-invasive brain stimulation started to inform each other's experiences and converged on the recognized importance of considering networks of regions. The study presented in **Chapter 7** serves as a perfect example of integrating this knowledge within the framework of connectivity-based neuromodulation. In a proof-of-concept study with healthy volunteers, we investigated whether the networks of effective OCD DBS targets (i.e., STN and NAc) could be modulated non-invasively. To this end, we reconstructed individual structural connectivity patterns from these sites to the cerebral cortex, defining accessible TMS targets as those displaying the strongest subcortical connectivity. Using an offline, sham-controlled TMS-functional MRI paradigm, we investigated the effects of stimulation on the functional connectivity networks of the deep-targets that we aimed to reach. Our results nicely align with what reported in the literature, while providing novel evidence potentially relevant for personalized brain stimulation for OCD treatment, as discussed in the following section.

2. Network-based personalization of brain stimulation treatment

The lack of tailoring on the individual patient is the primary limitation of current brain stimulation treatments, particularly concerning the choice of a likely effective stimulation target. Considering the heterogeneity in both phenomenology and neurobiology, the need for more personalized interventions is specially pressing for OCD patients. To date, no official guidelines are however available to suggest where to implant an electrode or place a stimulating coil based on certain patient's characteristics. In both the DBS and TMS literature, different meta-analyses and systematic reviews attempted comparisons across stimulation targets, however failing to find a clear superiority of one over the other (44-47). Overall, the interindividual variability in reaching the desired clinical effects remains high (47, 48), emphasizing the limitations of a "one protocol/target fits all" kind of approach to brain stimulation treatment. In the context of TMS for OCD, factors like individual anatomy, state-dependent effects and network-effects of stimulation, if left unaccounted, have been suggested to partly explain the variable response to treatment (47). On the path to personalized stimulation, addressing these issues is crucial, and promising approaches have already emerged. Two approaches are particularly relevant in the present discussion: anatomy-based and/or symptom/biotype-targeted definition of the stimulation site (47-50).

The first approach to personalized stimulation bases the selection of the stimulation target on individual anatomy, guided by structural and/or functional features. This procedure relies on the acquisition of an appropriate MRI protocol, and on the use of neuronavigation techniques to ensure accurate coil placement (51, 52). The idea of

using neuroimaging to improve precise spatial localization and account for anatomical individual differences has long been introduced, and measurable differences on the effects of stimulation reported (52-54). Traditionally, this approach employed either anatomical scans or functional localizer tasks, specifically designed to activate the target region (55, 56). Parallel to the importance of considering regions in connection rather than in isolation, connectivity-based selection procedures for TMS target definition have later emerged (57-59). Here, the idea is to identify a cortical stimulation site connected to a key subcortical region that would normally lay too deep in the brain to be non-invasively at reach. Harnessing the well-evidenced network effects of cortical stimulation (37-41), such connectivity-based approaches might increase the likelihood of effectively influencing subcortical structures with a key impact on clinical symptoms. Primarily investigated in the context of depression treatment, studies employing these procedures have pointed to large interindividual differences on where the coil should be placed to successfully modulate deep regions (57). Thus, attention should be clearly placed on reconstructing individual connectivity patterns leading to personalized stimulation targets. To date, most of these studies have relied on the functional connectivity of relevant sites (42, 57, 60), with only one study employing a tractography-guided approach (36). In **Chapter 7**, we demonstrate that reconstructing the structural connections of deep-brain nuclei key to OCD pathology leads to the identification of reliable cortical targets. Namely, with some variability across individuals, the identified stimulation sites were mostly located around the precentral/postcentral gyrus and middle frontal gyrus, in proximity to the targets employed in the TMS OCD literature or generally belonging to the same network (46). It remains to be established whether the large observed inter-individual variability in response to TMS for OCD could be reduced by using such individualized, connectivity-based approach to target selection. Additionally, an active discussion in the field should be initiated on the respective effectiveness of structural or functional connectivity-guided target selection, conducting formal comparisons between the different methods.

A second, ideally complementary, approach to personalized stimulation bases the selection of the stimulation target on the patient's "biotype" (60, 61). Here, the idea is to use stimulation (and its network effects) to influence the brain circuitries that are more likely affected in a particular patient, and more likely act on specific symptoms. For example, an interesting finding on the use of DBS for OCD treatment shows that electrical stimulation of the ventral capsule and the anteromedial STN led to a comparable decrease in OCD core symptoms, but to dissociable effects on cognitive flexibility and mood, substantiated by the differential connectivity patterns linking the two stimulation sites to the frontal cortex (62). While no relevant studies have been conducted for TMS use in OCD, the depression literature has recently shown that

different stimulation targets might be more effective in reducing different symptoms (60), thus highlighting the potential for this approach.

Resolving two fundamental issues is however preconditional to its application, implying (a) the clear mapping of the network effects of stimulation, and (b) the definition of appropriate network/circuit-based patient-clustering approaches. Considerable attention has been recently devoted to conceptualizing OCD as a heterogeneous disorder that might include distinct (as well as overlapping) pathophysiological brain models (63). Shephard and colleagues (2021) recently proposed a neurocircuit-based taxonomy, discussing five main brain circuitries linked to OCD (i.e., sensorimotor, dorsal cognitive, ventral cognitive, ventral affective and fronto-limbic circuits) in relation to the clinical cases that they might better explain, and to the treatments that aim to target them (63). In **Chapter 7**, we show that TMS at two cortical sites differently connected to the STN and the NAc modulates the functional connectivity between these nuclei and other regions in the brain. Notably, the modulated clusters critically participate e.g., to the sensorimotor, ventral affective and fronto-limbic circuits, thus highlighting the potential relevance of this approach for the treatment of OCD. Additionally, we observe the engagement of both overlapping and segregated functional networks across the two considered stimulation sites. According to a neurocircuit-based taxonomy, and in the spirit of biotype-guided stimulation, it could thus be argued that one stimulation target might be more effective than another, depending on the prevalent neurocircuit and/or behavioral dysfunction of the individual patient.

However, criticism has been raised on the feasibility of this approach in psychiatry, where clusters of diagnostic symptoms do not easily map to distinct biological bases (64). The neuroscience field has acknowledged the possibility that patients' "biotyping" approaches might not necessarily lie within the boundaries of diagnostic categories. Rather, psychopathology might be better conceived in terms of varying alterations in major functional domains, which encompass cognition, social processes, arousal/regulatory systems, negative and positive valence systems (65). The Research Domain Criteria (RDoC) offers a framework to investigate these core systems on multiple levels, using different techniques and, importantly, accounting for a dimensional approach, to ultimately lead to better prevention, diagnosis and treatment (65). Even within traditional diagnostic categories, this framework can be useful to study and understand each psychiatric disorder (also) in terms of alterations in transdiagnostic markers.

In the context of biotype-targeted stimulation, identifying the neural basis and dimensional alterations in transdiagnostic domains can be relevant. For example, in **Chapter 2**, we demonstrate dissociable neural bases of a depression-related and an

anxiety-related subscale of neuroticism, beyond what is explained by the overlap of this construct with depression and anxiety state symptoms. In OCD, association studies point to higher levels of neuroticism among OCD patients (8-11), which some evidence relates to higher symptom severity (66, 67) and lower remission rates (68, 69). However, the potentially differential relationship between the multiple facets of neuroticism and OCD diverse phenomenology has not been investigated. Beyond neuroticism specifically, more research could be devoted to characterizing the relationship between trait and state markers, and how they map to the brain differently across patients (as outlined in section 4. Future directions). In our study, we show an association between higher neuroticism-depression/anxiety scores and reduced whole-brain connectivity of many cortical regions. This might be particularly interesting in the context of non-invasive stimulation, offering potentially easy-to-reach targets for TMS use. In **Chapter 3**, we demonstrate alterations in the organization and connectivity of network hubs of OCD patients. Focusing on hub regions has been an active line of research in the context of OCD neurobiology, and evidence has pointed to the critical role of e.g., the precuneus (70, 71), inferior parietal lobule (72) or cingulate cortex (73), known for their extensive connectivity towards cortical and subcortical regions. Of note, these regions critically participate to rich-club organization, as identified by our as well as previous studies (74-76). Considering the extensive reciprocal connections that these regions tend to establish, and their critical role in global neural communication (12, 74, 77), stimulating one of these hubs might have considerable impact on the rest of the network. As a matter of fact, the only FDA approved TMS protocol for OCD places a deep coil over the medial prefrontal cortex/dorsal anterior cingulate cortex (78, 79). Procedures using standard TMS coils could select the stimulation target based on optimal connectivity to relevant network hubs (e.g., cingulate) placed deeper in the brain and otherwise not directly accessible.

3. Implications of (non-)stimulation: OC symptoms and beyond

For an individual affected by OCD, accessing neuromodulation interventions in the form of invasive or non-invasive brain stimulation implies a history of numerous failed treatments. DBS and TMS are only reserved to patients that still experience severe, incapacitating symptoms despite various attempts with standard approaches, in the form of repeated trials of psychotherapy and/or pharmacotherapy (80). For someone enduring a great deal of suffering, with essentially no alternative options left, the impact of undergoing these procedures can be major. Sometimes, the simple act of receiving these treatments is significant by itself.

A whole dedicated field focuses on understanding and quantifying the impact of factors other than the intervention per se. These factors mostly fall under the definition of placebo or nocebo effects (81), driven by someone's expectations (positive or negative) towards the effect of a treatment. Neuromodulation procedures are not exempted from these effects (82). On the contrary, evidence suggests a linear relationship between the invasiveness of an intervention and the magnitude of the elicited placebo response (83). Accordingly, several findings convincingly show the existence of these effects in the context of DBS treatment for Parkinson's disease (84-86). Given the current lack of systematic investigations in DBS for OCD, in **Chapter 5** we summarize the evidence from existing randomized, controlled trials to quantify changes in OCD symptoms that might not be due to electrical stimulation of the brain. Results demonstrate that improvement following a period of inactive stimulation amounts to a 15% reduction in symptoms severity, which can already constitute a meaningful difference in clinical terms (87).

Yet, treatment success is generally defined as a 35% reduction from baseline in the severity of OC symptoms. Certainly, reducing the occurrence and impact of obsessions and compulsions is and shall remain the primary goal of an intervention in the case of OCD patients. However, brain stimulation treatment can also give rise to a wide range of additional experiences that can meaningfully impact the life of patients (88). In **Chapter 6**, we attempt to explore and categorize them, specifically focusing on the effects beyond the OCD sphere. Semi-structured interviews with operated patients and their relatives reveal a wide variety of positive changes in their life, mostly in the form of improved mood and calmer behavior, but also feelings of increased confidence, competence, sensitivity towards their inner emotions and towards others. At the same time, individuals can experience undesired changes such as sleep problems, difficulty with memory or concentration. Importantly, both consistencies and differences exist across patients, highlighting the importance of addressing each individual experience.

Comprehensive knowledge on the full range of effects that could be expected following brain stimulation, and on additional factors that could be contributing to driving them, is relevant in different ways across the research and clinical contexts. For example, in a clinical setting, factors unrelated to the actual procedure but with a knowingly positive impact (e.g., expectations of benefit) (**Chapter 5**), could be harnessed to increase the patient's motivation and response. Conversely, the same knowledge can be used to implement effective study design strategies that appropriately control for the factors confounding the target effect. Knowledge of the full range of experiences accompanying the treatment (**Chapter 6**) can in fact also contribute to this purpose, when used to improve shared decision making on undergoing the procedure and to help manage the patient's expectations about life following surgery. Finally,

insight into various treatment effects can guide the development and choice of appropriate assessment tools to longitudinally capture a broad range of experiences beyond OC symptoms.

Based on the results presented in **Chapter 6**, we highlight the importance of helping operated patients navigate their new self and experiences, for example by including psychotherapy in the DBS treatment package. Ensuring timely monitoring and support might be even more crucial when traversing difficult times. In the past couple of years, the COVID-19 pandemic posed considerable strain on everyone's wellbeing, drastically changing our everyday life, health and social relationships, and potentially aggravating the condition of those already experiencing mental health problems. In **Chapter 4**, we review the first literature available addressing the potential worsening of symptoms in OCD patients, particularly those concerned with contamination obsessions, as a result of the enforced restrictions and hygiene recommendations. Although results do not recognize this subtype at a particular risk, the vulnerability of the whole OCD population to an increase in symptoms severity was recognized (89-94). Yet, reports of stable symptoms status or even experienced improvement exist (94, 95). In this regard, we consider access to treatment or psychological support as one of the key factors that might contribute to explain different individual trajectories. While this is certainly a universal need, it can become especially urgent for those patients that are currently traversing existential changes following an invasive procedure.

4. Future directions

We here specifically highlight how the results of the present thesis could guide future investigations in the context of symptoms network-mapping and personalized brain stimulation treatment. In many of its parts, this thesis indeed provides preliminary evidence that leaves room for many more questions.

Anxiety and depression trait and state network mapping. Personality traits like neuroticism can serve as vulnerability factors to developing or worsening psychiatric symptoms (5, 96-98). Although demonstrated primarily in anxiety and depression disorders, the relationship exists across a range of diagnostic categories (6, 7, 99). In **Chapter 2**, we demonstrate that neuroticism maps to multimodal brain markers, beyond what explained by its overlap with clinical depression and anxiety state symptoms. More importantly, in line with previous suggestions (97), we show that neuroticism might be better understood as a multifaceted construct, identifying partially distinct brain correlates of an anxiety- and a depression-related subscale of the total score. OCD has been generally associated with higher levels of neuroticism (8-11), in turn related to higher symptom severity (66, 67) and lower remission rates (68, 69). Of

note, OCD is a highly comorbid disorder, primarily accompanied by anxiety disorders or major depression disorder (100). Thus, anxiety and depressive symptoms generally co-occur with obsessions and compulsions, in some instances confounding brain-based investigations (101). Future studies could address how trait and state anxiety and depression map to the brain networks of OCD patients, how they relate to core symptoms differently across patients, and whether this relationship influences clinical response to brain stimulation treatment.

Phenotype of altered rich-club organization. Alterations in the rich-club organization of the brain have been linked to a range of psychiatric and neurological disorders, highlighting the transdiagnostic nature of this property of brain organization (102). In **Chapter 3**, we show a decrease in rich-club organization in unmedicated OCD patients. Consistent with the idea of a transdiagnostic rather than disorder-specific brain marker, our results find no correlation with clinical scores of OC symptoms (or individual symptom dimensions). Given the fundamental role in neural integration, communication and higher-order cognitive processes (77, 103, 104), future studies should investigate whether a decrease in rich-club organization relates to specific cognitive impairments, or associates with a certain neuropsychological profile. This might be particularly relevant in the context of symptom/biotype-targeted stimulation. We previously discussed the potential value of using network hubs as brain stimulation targets, given their extensive connections between each other and other regions of the brain. Targeting a rich-club node might be beneficial for patients presenting a set of cognitive impairments compliant with those (eventually) associated with altered rich-club organization.

Predictors of clinical response and full range of associated experiences. Given the invasiveness of DBS treatment, the need for reliable predictors of response is specially pressing. Different meta-analyses mostly unsuccessfully attempted to link clinical patient characteristics to the observed improvement in OC core symptoms, or secondary outcomes of DBS treatment (e.g., depressive symptoms, quality of life). As reviewed in previous sections, the search for correlates of good response then moved to brain connectivity markers (18-21), although their predictive value still needs appropriate cross-validation (105). Overall, the focus has primarily been on the prediction of improvement in obsessions and compulsions. However, results from the present thesis encourage the field to consider the full range of elements and experiences that accompany DBS treatment. In **Chapter 5**, we demonstrate that factors other than the actual stimulation of the brain via the DBS implant can reduce the severity of OC symptoms, in a relatively clinically meaningful way. In **Chapter 6**, we show the wide variety of positive and negative experiences that characterize the life of patients years after surgery. We suggested how this knowledge can be used to guide the choice and the

development of assessment tools that appropriately capture this variety. If eventually linked with pre-operative patient characteristics, systematic data on DBS experience across centers and anatomical locations would help delineate the profile of a DBS candidate as a person most likely to overall benefit from DBS, with the least probability of experiencing adverse effects.

Personalized, connectivity-based TMS for OCD patients. The results of the present thesis have been overall discussed in the framework of developing personalized brain stimulation treatment for OCD patients. In **Chapter 7**, we conducted a proof-of-concept study testing the feasibility and effect of a connectivity-based individualized procedure in a group of healthy volunteers. In light of the obtained results, we deem this approach worth investigating further. First, the reproducibility of the reported network effects of TMS should be evaluated by employing the presently tested set-up in a group of OCD patients. Given the evidenced alterations in the OCD brain network's structure and function, it cannot be excluded that the same procedure might elicit different network effects in patients compared to healthy individuals. Upon confirming its relevance to the OCD patient population, this connectivity-based procedure can be used to define personalized stimulation targets within the framework of a neurocircuit-based taxonomy of OCD (63), where patients can be assigned to different stimulation conditions that target the neurocircuit most likely affected. Superiority trials are then necessary to allow formally quantifying the advantage of this tailored approach over the standard selection of one common stimulation target.

5. Methodological considerations

Throughout the different chapters, we employed a variety of different methods, ranging from multimodal neuroimaging to narrative and meta-analytic reviews of the literature, qualitative methods and the application of brain stimulation. Each of these techniques bears its own limitations, and results stemming from their use should therefore always be interpreted keeping probable sources of bias in mind.

Potentially problematic to neuroimaging and connectome-based studies in particular, is the multitude of methodological choices that determine the acquisition and processing of the imaging data, the construction of the network, and the implementation and interpretation of measures reflecting its properties. Increasing the degrees of freedom of the analysis process inevitably complicates the framing of new findings against the available evidence, particularly when relatively scarce in number and methodologically heterogenous. As a result, contradicting findings are often blamed on the technical diversity of the study that generated them. While this can certainly be a source of ambiguity, this variability is anyway relevant, if not necessary, when

attempting to establish the true biological validity of a certain construct. In the absence of a gold standard set out to follow, the scientific reliability of any result indeed lies within their stability and replicability across a variety of technical choices with equally valid pro and counterarguments. We thus underscore the relevance of studies that aim to tackle an emerging question from a different angle; while this is often intended in terms of different study populations, we highlight the value of employing diverse methods as a validation strategy.

In doing so, we urge the reader of this and others' work to refrain from inferring causality from measures of connectivity, reminding that structural and functional connectivity are inherently limited in their ability to reflect causal relationships between regions. Currently devised methods do not allow to discern the directionality of white-matter tracts, while functional connectivity relies on highly time-dependent statistical relationships that do not imply causality (106). Similarly, when assessing remote effects of brain stimulation, reconstructing the causal chain of events leading to observed network effects is extremely complex, and must consider the potential role of a series of covarying or confounding factors (107). In many cases, connectivity measures are used as descriptive snapshots of certain brain properties, often considered (particularly when relying on structural connectivity) as stable, invariant characteristics of network topology. However, this is not the case. Structural and functional connectivity rather change over a range of time and spatial scales, sensitive to context, time or activity (108, 109). For this reason, models that track dynamic changes of connectivity are thought to offer a more appropriate characterization and adequate understanding of brain networks. Although not addressed in the current thesis, effective connectivity is particularly relevant in this regard. By generating and comparing the statistical evidence of different mechanistic models, effective connectivity attempts to describe directed causal links between network elements, focusing on the transient, adaptive and context-sensitive nature of network connections (109, 110).

While connectomic and graph theoretical analysis have almost unlimited application potential in research studies, their translational value in the clinical context faces some constraints. In the present chapter, we extensively discuss the scientific relevance of employing connectivity-based approaches to TMS target selection. In clinical practice, as well as in several clinical trials (47), currently the identification of the stimulation target is hardly based on MRI scans, mostly relying on the international 10-20 EEG cap system or on scalp measurements (111, 112). At the expenses of anatomical tailoring and precision, this approach has however the considerable advantage of being fast and cheap, and thus easily implementable in clinical practice. Conversely, following a connectivity-based procedure for stimulation target selection relies on a lengthy and costly process, requiring considerable expertise and

computational resources. Thus, formal comparisons and cost-effectiveness analyses should critically instruct us on the real advantage of personalized as compared to standardized target selection methods.

6. Conclusions

Results stemming from this dissertation generally align with the needs that the field has been expressing: (a) to look at brain regions as embedded in a complex network; (b) to apply this framework to the study of the brain, crossing the boundaries of diagnostic categories, as well as of brain stimulation mechanisms and effects; and (c) to integrate the knowledge from both fields to design and guide personalized brain stimulation treatment.

The present thesis was framed, and its results discussed, with the goal of personalized brain stimulation treatment for OCD in mind. In many of its parts, this thesis contributes to this objective with preliminary knowledge that needs further exploring. After laying a few building blocks that are necessary along the way, we underline the importance of continuing on this road.

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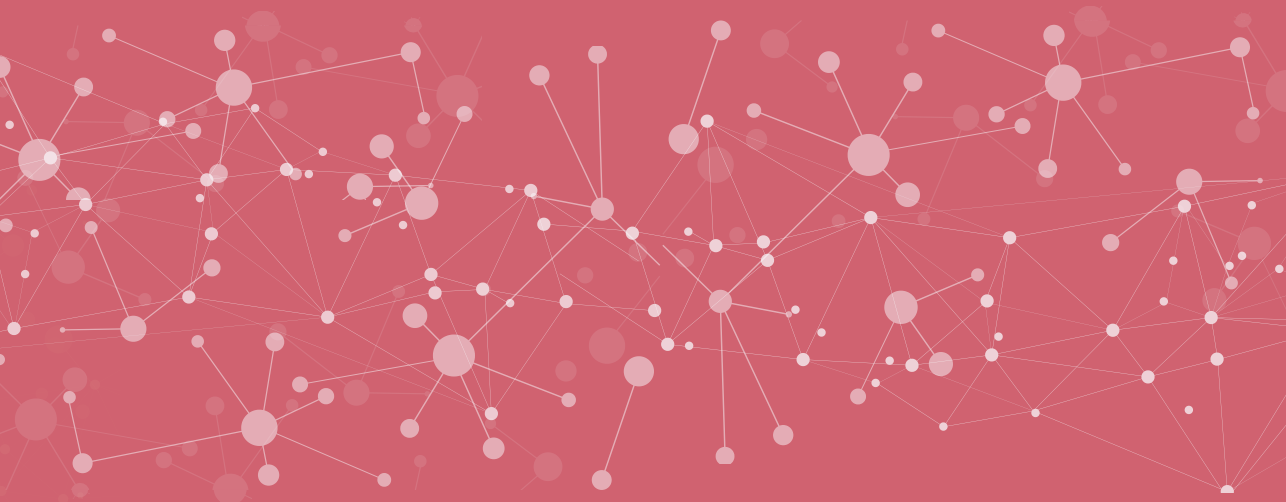
APPENDIX



SUMMARY

Obsessive-compulsive disorder (OCD) is a debilitating psychiatric condition, where patients experience distressing thoughts or impulses (i.e., obsessions), generally accompanied by rigid mental or behavioral rituals (i.e., compulsions). A non-negligible portion of individuals fails to respond to standard treatments and becomes eligible for neuromodulation interventions, in the form of invasive or non-invasive brain stimulation. Considering the high heterogeneity in the phenomenology and neurobiology of OCD, tailoring the intervention on the single patient is crucial. Unfortunately, there is currently no clear solution to this problem.
On the path to developing and applying personalized brain stimulation treatment, several questions first need to be answered. The notions and the approach that the neuroimaging and neuromodulation fields have progressively acquired and adopted (Chapter 1), dictate the issues that researchers in the field should be addressing. The present thesis aimed to tackle a few related considerations.

Any effective personalized brain stimulation intervention relies on effective patient-clustering approaches, e.g., enabling to answer questions like, which stimulation target is best for which patient? Given the complexity and heterogeneity that characterize OCD manifestations, it first needs to be clear how different aspects of symptomatology are represented in the brain. In this regard, decades of neuroimaging research demonstrated the importance of mapping changes in the organization and function of brain networks, rather than considering regions in isolation. In doing so, the field parallelly moved from a disorder-specific to a trans-diagnostic perspective to understanding psychiatric disorders. Following this evolution, in the first part of this thesis, we investigated psychological, neural and environmental aspects that have been linked to OCD, but generally span different diagnostic categories.

In **Chapter 2**, we characterized the brain basis of neuroticism, the single vulnerability factor most consistently linked to psychopathology. We employed a large, population-based sample from the UK Biobank Imaging study. We investigated the relationship between multimodal brain measures (i.e., activation during an emotional face processing task, resting-state nodal degree, gray matter concentration, fractional anisotropy) and different facets of neuroticism (i.e., a depression-related and an anxiety-related subscale), while controlling for state symptoms of depression and anxiety. Results show both unique and overlapping correlates of the two neuroticism components, validating their distinction on a neural level across imaging modalities. We considered both cross-sectional and longitudinal neuroticism, highlighting the stability of this trait and its components over time by reporting significant brain correlations with longitudinal mean scores, but not with change scores between assessment visits. In general, the results align with the recognized need of looking at widespread regions of

the brain to characterize the brain basis of neuroticism, beyond traditional conceptualizations circumscribed to a few areas.

In **Chapter 3**, we investigated alterations in a fundamental property of brain networks organization and function (i.e., rich-club organization) in unmedicated OCD patients and a group of their unaffected siblings. Rich-club organization refers to the property of topologically central regions of the brain to establish strong and numerous connections between them, enabling information to be integrated quickly and efficiently. Results show decreased rich-club organization and rich-club connectivity density in OCD patients compared to healthy controls, suggesting that brain hubs exhibit less connections between them, and do not necessarily allocate the strongest weights thereto. Rather, our findings point to differences in the topological arrangement of connections and their weights, with OCD patients seemingly allocating more weight to peripheral connections at the detriment of the rich-club core. Preliminary findings of increased rich-club organization in unaffected siblings suggest a possible resilience mechanism to investigate further.

In **Chapter 4**, we reasoned on the possibility that OCD patients (particularly of the contamination/washing subtype) might be at exceptional risk of increased symptom severity during the first wave of the COVID-19 pandemic, when strict hygiene measures and recommendations were heavily enforced. We reviewed the available evidence investigating whether such relationship would exist. Although affirmative answers have been reported, the evidence reviewed did not convincingly ascribe a crucial role to COVID-19 preventive measures in driving symptom exacerbation in OCD patients, nor recognized those with contamination obsessions as being at increased risk.

Any effective personalized brain stimulation intervention also relies on in-depth knowledge of currently used applications and their mechanisms of action. In this regard, the neuromodulation field has grown to acknowledge that local stimulation always implies the modulation of connected networks, in a way that is likely crucial to driving symptoms improvement. Insight into the full range of elicited effects, and the factors that might be driving them, is fundamental to tailoring an intervention, as well as informing, monitoring and supporting the patient throughout the treatment. Thus, in the second part of this thesis, we first evaluated a few aspects related to the use of invasive brain stimulation for the treatment of OCD. We finally explored a connectivity-based approach to guide non-invasive stimulation target selection in an individualized manner.

In **Chapter 5**, we quantified the clinical effects of deep-brain stimulation (DBS) treatment for OCD that are not due to the electrical stimulation of the brain. We conducted an individual-patient data meta-analysis of published, randomized, sham-controlled trials, primarily employing a cross-over design. We calculated the

improvement in OC symptoms that followed a period where stimulation was inactive (i.e., sham stimulation), while checking for the occurrence of period effects. Results show a significant change in the clinical score of symptoms severity following sham stimulation, amounting to a 15% reduction. We further highlight the likely occurrence of period effects, reasoning on how this can impact design strategies for future randomized trials.

In **Chapter 6**, we categorized a wide variety of positive and negative experiences associated with DBS treatment for OCD. We conducted semi-structured interviews and performed content-analysis on what reported by operated patients and their relatives, between five weeks to ten years following implantation. Results point to a wide variety of psychological and physical side-effects of DBS, beyond specific changes in OC core symptoms. We record positive experiences manifesting as improved mood and calmer behavior, but also negative changes such as impaired memory and concentration and sleep problems. Overall, findings suggest that patients can feel and behave significantly different towards themselves and others, and highlight the importance of systematically assessing the full range of DBS effects throughout the course of the treatment.

In **Chapter 7**, we investigated the effects of a personalized, connectivity-based transcranial magnetic stimulation (TMS) procedure on the functional networks of deep-brain targets relevant to OCD pathology. Based on the evidence that cortical TMS can influence remote regions, we aimed to modulate non-invasively the subthalamic nucleus (STN) and the nucleus accumbens (NAc), generally used as targets for DBS in the treatment of OCD. To this end, in each individual we identified two personalized TMS targets based on the structural connectivity patterns linking the STN/NAc to the cerebral cortex. In order to assess modulation of the deep-brain nuclei, we investigated TMS-induced changes in their resting-state functional connectivity towards other regions of the brain, using a sham-controlled, offline TMS-functional magnetic resonance imaging (MRI) procedure. Results show both static and dynamic signatures of functional connectivity changes of both STN and NAc, with overlap and differences in the engaged networks across stimulation targets. Given the relevance of these networks to OCD pathology, we consider an individualized, connectivity-based TMS procedure as a potentially interesting avenue to further explore in the context of OCD treatment.

IMPACT PARAGRAPH

OCD affects nearly 3% of the general population worldwide (1), ranking as the fourth most common psychiatric disorder (2) and amongst the twenty most debilitating diseases (3). Afflicted patients are limited in many aspects of their life, struggling to complete ordinary tasks, likely becoming socially isolated, unable to work or live independently (4). If left untreated, OCD often follows a chronic course with fluctuating symptoms severity, and is generally associated with a marked reduction in quality of life, increased financial burden and mortality (5, 6). A 2010 analysis of the economic costs of mental disorders estimated 2.9 millions affected individuals across European countries, for a cost of 779 euros per capita and 2272 million euros in total (7). Thus, ensuring effective care is of the utmost importance, primarily to the sufferers of this debilitating condition, and consequently to society as a whole.

While optimal use of psychotherapy and pharmacotherapy effectively relieves symptoms in the majority of individuals, up to 30-40% fails to respond to standard treatment approaches (8). These patients remain severely symptomatic, experience a great deal of suffering and maintain a considerably low quality of life. For them, deep brain stimulation (DBS) is an established last-resort option. Its efficacy has been repeatedly and independently demonstrated by rigorous, blinded randomized trials across centers, device manufacturers and anatomical site of implantation (9). Being covered by Dutch insurance for the treatment of refractory OCD, DBS is an effective option thus equally accessible to severe patients regardless of their social or economic extraction. Yet, the small number of OCD patients undergoing surgery stands in stark contrast with the six-figure count for the treatment of neurological disorders (e.g., Parkinson's disease) (10).

One of the reasons hindering wider applications of DBS is the skepticism and concern that many psychologists, psychiatrists and patients hold towards an invasive surgery (10-12). Primarily ascribed to a lack of knowledge (12), this hesitation could then be reversed by ensuring e.g., open dissemination and access to relevant scientific papers, continuous training and education opportunities for clinicians enabling referral, appropriate patient consultation or support groups connecting potential DBS candidates to operated patients. In this regard, results from the present thesis (**Chapter 5, 6**) are thus noteworthy, aiming to increase knowledge and awareness about the DBS procedure and what it entails. In both studies, we provide concrete recommendations or explicit suggestions for research as well as clinical implementations, aiming to increase patient's critical judgement, response, monitoring and support. With the study in **Chapter 5** already published in an open access journal, the results from **Chapter 6** will similarly be disseminated according to the principles of open science, facilitating the usability of the results.

The long list of stringent criteria restricting patients' eligibility is another limiting factor to a wider use of DBS. To qualify for treatment, OCD patients must classify as treatment-resistant, implying the failure of at least two trials of selective serotonin-reuptake inhibitors at a maximum tolerated dose for at least 12 weeks; one trial of clomipramine at a maximum tolerated dosage for at least 12 weeks; one augmentation trial with an antipsychotic for at least 8 weeks in combination with one of the aforementioned drugs; and one complete trial of cognitive-behavioral therapy (CBT) including exposure and response prevention (ERP) confirmed by a psychotherapist (9). Next to boosting access to DBS for eligible patients, the field has thus every incentive to improve less invasive treatment options, in the hope for them to be accessible to a wider patient population.

Transcranial magnetic stimulation (TMS) treatment is established in the context of depression and explored for several other psychiatric indications (13). In light of the positive findings in OCD (14), the field developed a strong interest in understanding how TMS can be best used for these patients. A TMS protocol employing deep coils has received US Food and Drug Administration approval and Conformité Européenne mark in 2019 (15, 16). However, while covering TMS treatment for depression, in the Netherlands healthcare providers do not reimburse TMS treatment-related expenses for OCD, rendering access to this therapy potentially difficult and dependent on financial means. To eventually change these policies, the research field has been actively attempting to solve some of the ambiguities still surrounding the procedure, aiming to increase the success rate and reported efficacy in OCD patients. For example, a Dutch nationwide multi-center randomized clinical trial (TETRO) has been founded to investigate the added value of TMS when combined with ERP for patients that do not show sufficient response to ERP alone or combined with medication (ClinicalTrials.gov Identifier: NCT05331937). Else, another founded Dutch clinical trial (TIPPICO) seeks to compare the clinical and neurobiological effects of three different stimulation protocols during an 8-week CBT-TMS combined treatment (ClinicalTrials.gov Identifier: NCT03667807). Beyond national borders, ClinicalTrials.gov counts 21 currently active clinical trials worldwide investigating various aspects of TMS use in OCD. Clearly joining this effort, the present thesis has overall focused on how brain stimulation treatment could potentially be tailored on the individual patient, under the hypothesis that more personalized procedures could reduce the highly variable clinical response to TMS registered in many trials (17, 18). In many of its parts, this thesis offers preliminary evidence, contributing at different levels and in different ways to this overall objective. Particularly in **Chapter 7**, we actively step in this direction, directly translating current developments of the TMS depression literature to the OCD framework. By employing a connectivity-based approach to define personalized

stimulation targets, we provide important preliminary results on the potential relevance of this procedure to address OCD brain pathology in an individualized manner.

Overall, in the studies here presented, we embedded our research questions, methodological approaches and interpretation of the findings into the framework and the needs that the field has long expressed, confirming their relevance to the study of the (OC) brain and the implementation of brain stimulation techniques. By disseminating our results in scientific conferences and open-access peer-reviewed international journals, and by clearly highlighting how the provided knowledge can guide future investigations, the scientific and clinical impact of this thesis on the path to personalized brain stimulation treatment for OCD is immediately clear.

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CURRICULUM VITAE & LIST OF PUBLICATIONS

About the Author

Samantha Baldi was born on May 14th 1994 in Gavardo, Italy. In 2013, she completed secondary education at Liceo Enrico Fermi, Saló. In 2016, she obtained a Bachelor's degree in Sciences and Techniques of Cognitive Psychology at the University of Trento, Italy. She then moved to The Netherlands, where in 2018 she obtained a Research Master's degree in Cognitive and Clinical Neuroscience, with a specialization in Neuropsychology at Maastricht University. Continuing on the path undertook during her Master's research internship, she started her PhD in 2018 at the Department of Psychiatry and Neuropsychology of Maastricht University, under the guidance of Prof. Dr. Koen R.J. Schruers, Dr. Liesbet Goossens and Dr. Teresa Schuhmann. During this time, she spent three months at the Department of Psychiatry of the University of Cambridge, United Kingdom, working in the laboratory of Prof. Dr. Valerie Voon. She will proceed her career working as post-doc at Brigham and Women's Hospital, Harvard Medical School, Boston, USA.

List of Publications

Peer-reviewed journal articles:

Baldi, S., Michielse, S., Vriend, C., van den Heuvel, M. P., van den Heuvel, O. A., Schruers, K. R., & Goossens, L. (2022). Abnormal white-matter rich-club organization in obsessive-compulsive disorder. Human Brain Mapping, 43(15), 4699-4709.

Baldi, S., & Schruers, K. (2021). Expert opinion in Obsessive-Compulsive Disorder: Could protective measures for COVID-19 contribute to the worsening of OCD symptoms? Personalized Medicine in Psychiatry, 27, 100076.

Schruers*, K., **Baldi*, S.,** van den Heuvel, T., Goossens, L., Luyten, L., Leentjens, A. F., ... & Viechtbauer, W. (2019). The effects of deep brain non-stimulation in severe obsessive-compulsive disorder: an individual patient data meta-analysis. Translational Psychiatry, 9(1), 183.
**These authors contributed equally*

Manuscripts submitted, in revision or in preparation:

Baldi, S., Schuhmann, T., Goossens, L., & Schruers, K.R. Individualized, connectome-based, non-invasive stimulation of Obsessive-Compulsive Disorder deep-brain targets: a proof-of-concept study. *Under review in NeuroImage.*

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Baldi, S., Zhao, Y., Goossens, L., Schruers, K.R., & Voon, V. Multimodal brain correlates of neuroticism: distinct and overlapping contributions of depressive and anxious traits. *In preparation.*

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