On connecting dots

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.