On connecting dots

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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