Editorial Commentary

Precision surgery for obsessive compulsive disorder—which is the proper target?

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Obsessive-compulsive disorder (OCD) is a mental health condition in which recurring, anxiety-inducing thoughts or urges (obsessions) are usually followed by uncontrolled mental or behavioral acts (compulsions) being the cause of major illness related disability (1). Patients diagnosed with OCD resistant to medical and psychiatrical treatment may be contemplated for surgery. The original operations sought to produce lesions at different points within the circuit of Papez (considered the substrate of emotions) such as the cingulate bundle, the anterior thalamo-cortical connections or the anterior limb of the internal capsule (ALIC), among others (2). However, the results of these operations, regardless of the target chosen, ranged about 50% of good results. Curiously, the same lesions applied to a different psychiatric disease, major depression, yielded similar outcomes. Deep brain stimulation (DBS) for OCD has been later introduced to substitute the lesioning procedures, the main arguments being that the possible side effects of the technique can be reverted by turning the stimulator off, and that the therapeutic effect can be modulated by changing the stimulation parameters. DBS for OCD has targeted regions similar to those formerly subjected to lesions, which are considered components of the reward and motivation system, such as the nucleus accumbens (NAcc), the ventral capsule/ventral striatum (VC/VS), the anteriomedial (limbic) portion of the subthalamic nucleus (amSTN), the ALIC, the inferior thalamic peduncle and the bed nucleus of the stria terminalis (BNST), which are among the components of the motivational and reward system (3,4).

However, the clinical results of DBS to control OCD symptoms do not greatly improve those of the lesions. Most recent meta-analyses (5) reveal that the overall clinical response achieved by stimulation of the different targets is about 50–60% of clinical responses. In order to compare two different targets of stimulation, our group started a clinical trial in which DBS electrodes were placed in both amSTN and accumbens nuclei (6). Checking the different combinations of activated electrodes, we observed that it was not a single nucleus the most effective one for treating the symptoms. However, while the reports of unilateral stimulation of the accumbens nuclei had suggested that it was sufficient to stimulate the right side (7), our first patients responded best to stimulation at the left side in both nuclei. Data seemed to suggest that the right side was not the right side to stimulate, but that it was different for different patients.

Tyagi *et al.* have reported on a prospective double-blind study comparing two different targets for OCD: the VC/VS and the amSTN. Patients were consecutively entered in phases of stimulation of either the amSTN or the VC/VS DBS during 12 weeks, followed by a stimulation phase of both targets during another 12 weeks. They observed no major differences in outcome, measured by the Yale-Brown Obsessive-compulsive scale (Y-BOCS), between the two targets, and only a marginal additional improvement when both were simultaneously stimulated. However, they noted

a differential improvement with both targets in terms of cognitive flexibility or mood. The stimulation of amSTN best improved scores in cognitive flexibility. When they traced the structural connectivity of amSTN and VC/VS to the prefrontal cerebral cortex, they found that amSTN DBS was preferentially connected to the lateral orbitofrontal cortex, the dorsal anterior cingulate cortex, and the dorsolateral prefrontal cortex. On the contrary, VC/VS DBS was connected primarily to the medial orbitofrontal cortex and best improved mood. These findings could shed a light on the problem of the 50% limit of improvement curse.

OCD obsessions and compulsions include a heterogeneous range of contents (8). Rasmussen and Eisen (1994) suggested a model for subtyping OCD symptoms categorizing core features, including abnormal risk assessment and incompleteness, that could be useful to identify homogeneous subgroups that have distinct treatment responses (1). The contents of obsessions or compulsions shown by patients can be further categorized into four dimensions: contamination and washing, hoarding, symmetry and repeating or ordering, and forbidden thoughts and checking, and 74% of patients would fit into this classification (9). When challenged with images corresponding to these dimensions inside the magnetic resonance (MR), in the so-called Maudsley test (10), different areas of the prefrontal cortex are activated, which are specific for each symptomatic dimension. For example, patients who have contamination obsessions activate preferentially the ventromedial cortex, while those who check activate mainly the dorsolateral prefrontal cortex (11). These diverse areas of the prefrontal cortex project to the striatum into different areas ventrodorsally distributed, and not only to the NAcc, which is its most ventromedial part (corresponding to the VS). Ventomedial prefrontal and orbitofrontal cortices (50% of areas) project to the NAcc, but the anterior cingulate cortex and dorsolateral prefrontal cortex do not (12). If this is so, why should we surprised to find that only half of the cases of OCD improve if we stimulate in only one target (the NAcc) in every OCD patient?

In order to study the possibility that the optimal target for a given patient could be individualized related to the symptomatic content of his or her disease, we performed a prospective, randomized, double blinded study in 7 patients, candidates to DBS for OCD (13). We segmented the striatum using the projections from the ventromedial, the orbitofrontal and the dorsolateral) and the anterior cingulate cortex. A trajectory was planned to insert a tetrapolar electrode along the striatum in such a way that each contact was closest to each segment. Then, we stimulated the patients following a random series of five periods (the four contacts plus zero volts activation) for three months, each separated by one month washout period. Patients were evaluated by an observer who was blind to which contact was active. Of the seven patients studied, six patients (85.71%) were considered responders, with a median Y-BOCS reduction of 48.39% (mean 51.01%) using different electrode contacts, while only three (42.86%) would have responded if the accumbens contact (the most distal one) had been used, as usual, with a median Y-BOCS reduction of 41.18% (mean 23.99%).

Then, retrospectively, we evaluated if functional and structural connectivity measures would have predicted the optimal contact site. A Maudsley's challenge test (MOCSS) had been performed in fMRI before the operation, where pictures related to several symptomatic OCD contents were shown. The clinical results were compared with main symptomatic dimension of the patient and with the location of the best active contact in relation to the white matter projections to the striatum from the different active prefrontal areas during the MOCSS study.

Patients showing preferentially washing obsessions and compulsions (abnormal risk assessment) responded best to the more ventral contacts while those presenting symptoms to checking or ordering or with ideatory contents (incompleteness) responded best to the more dorsal contacts. Furthermore, there was a relationship between the presumed volume of tissue activation by each contact and the tracts projecting to the striatum from the cortical activated by area after the Maudsley's test.

These results, and those by Tyagi *et al.* [2019] suggest that there is a personalized proper target in DBS for OCD depending on the contents of the obsessions of each patient (14). Most of the studies judge DBS effect based on clinical outcomes (essentially, total Y-BOCS score) (15). However, the total Y-BOCS does not reflect the multidimensionality of OCD. Thus, it is difficult to identify which dimensions are reduced by DBS in terms of severity and disability. This would be the reason why different targets have a similar Y-BOCS score result. Probably, to test this, the Dimensional Yale-Brown Obsessive-Compulsive Severity Scale (DY-BOCS) (16), a clinician's ratings on current severity by symptom dimension should be used instead.

So, which anatomical structure is the proper target for

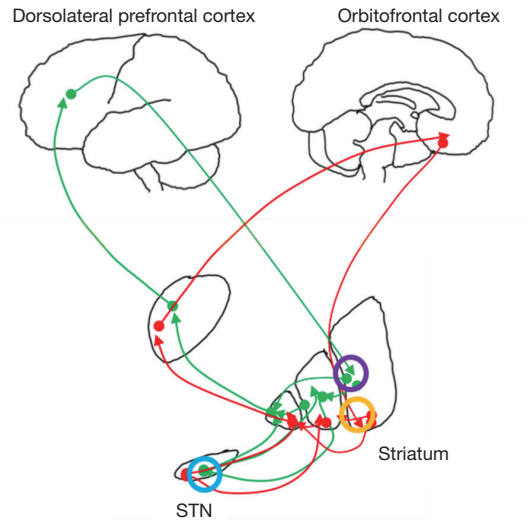

Figure 1 Idealised outline of the associative (green) and limbic (red) cortico-basal ganglia-thalamocortical circuits. Different subcircuits belonging to these loops could be targeted at different anatomical relay structures, choosing the ones which are specifically activated during the symptomatic challenge to the patient. The anteromedial subthalamic nucleus (STN) target used in Tyagi *et al.* (2019) (blue circle) would have influence mainly the associative circuit, improving cognitive flexibility, and the ventral capsule/ventral striatum target (orange circle) would have influenced the limbic one, improving mood. However, another target at the striatum (purple circle) could influence the associative circuit. Thus, the proper target is not located at a particular anatomical structure, but at the proper functional loop. Adapted from (17).

OCD?

Different cortico-basal ganglia–thalamocortical circuits have been described within the human brain, including the limbic, associative and motor ones. These circuits form loops travelling from the prefrontal cortex to the striatum (including the accumbens nucleus) and the thalamus through the anterior limb of the internal capsule and inferior thalamic peduncle, involving also the subthalamic nucleus (17). These circuits are intertwined into multiple interrelated spiral loops, rather than segregated pathways. Thus, possibly the proper target for a particular patient will be the specific subcircuit which is activated by the symptoms at the prefrontal or limbic cortex, at any of the different relays (cortex, internal capsule, striatum, thalamus, subthalamic nucleus), rather than the specific anatomical nucleus (*Figure 1*). This could explain the fact that several nuclei are equally efficient (or inefficient) anatomical targets for different patients included within the same "common OCD" box.

The next steps will probably consist in performing prospective studies using challenge functional tests, such as the MOCCS, and tracing the structural connectivity of the activated prefrontal areas to the target structure to stimulate the proper circuit within that structure, changing targeting in functional psychiatric surgery from an atlas-based anatomical fixed "one size fits all" methods for a functional, structural or effective connectivity based tool.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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