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RESEARCH HIGHLIGHT

Connectomic approaches to deep brain stimulation for OCD

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More than half a century ago, the field of human stereotactic neurosurgery was borne from the compelling need to treat patients with refractory forms of what we now call psychiatric disorders. In the late 1990s, deep brain stimulation (DBS) joined the therapeutic stage previously occupied solely by stereotactic lesion procedures. Obsessive-compulsive disorder (OCD) is the indication with the most clinical experience with DBS and the only one with a form of approval (via a humanitarian device exemption; HDE) from the US FDA. In the first two decades of this century, progress in DBS for OCD came in the form of a number of studies testing the efficacy of myriad brain targets, largely driven by empiricism. The last few years have witnessed an attempt to weave these narratives into a cohesive story, one that conceives of these potential targets not as isolated islands of disease, but rather as connected nodes in a dysfunctional network [1].

A series of recent papers summarized in Baldermann et al. [2] has attempted to build a parsimonious answer to the question of network targeting in DBS for OCD. They identify the connectomic profile of effective DBS contacts using normative tractography data (i.e., results derived from populations of healthy controls) to identify tracts associated with positive outcome. Their main finding is the prominence of a tract connecting the anterior cingulate cortex (ACC) and the region of the subthalamic nucleus (STN) that courses through the anterior limb of the internal capsule. Notably, all of these regions have been the target of DBS or lesion procedure for OCD, providing circumstantial evidence for their relevance. They suggest that this tract may represent a "hyperdirect" pathway between dACC and ventromedial STN in a manner analogous to the motor hyperdirect pathway that connects motor cortex to dorsolateral STN. This candidate tract was initially identified in outcome data from a single institution and then found to correlate with positive outcomes in datasets from several other institutions across a summed cohort of more than 100 patients.

The article in this issue by Widge et al. [3] subjects these efforts of Baldermann and colleagues to statistical scrutiny. In their own analysis of eight subjects' worth of data, Widge et al. used patient-specific (rather than normative) diffusion data for the connectomic analyses. Rather than simply taking the Baldermann model and testing for correlation within their dataset, they used various regression models to identify a relationship between candidate tracts and outcomes. In addition, they added statistical rigor by subjecting their models to formal multi-fold cross validation. The central message of their report is that none of the candidate tract models demonstrated *predictive* value of symptom improvement when tested in this statistically rigorous way.

Widge et al. point out important potential weaknesses in the previous efforts. Normative approaches tend to average out individual differences that may be critical for patient-specific targeting. Further, simply relying on correlative results does not guarantee predictive value, without which clinical relevance for prospective use is minimal. These concerns are partially allayed by a few notable factors. The multi-cohort nature of the previous work provides some confidence that independent groups, with their own targeting approaches, arrived at results whose connectomic profile bears at least some mutual resemblance. Further, although the power analysis and repeated measures design of Widge et al. are reassuring, the overall small sample size raises questions about generalizability across larger cohorts. Thus on one hand, debate over the relative importance of these perspectives and the apparently contradictory results may produce handwringing in the community.

On the other hand, one key common finding between Widge et al. and previous work could be a critical catalyst for advancement. Despite disagreement between patient-specific predictive value, both highlight the importance of fibers traveling between ACC and thalamic/subthalamic regions. The ACC is a key component of the cognitive machinery necessary for controlled decision-making [4]. When functioning optimally, this region helps allocate cognitive resources to decisions at hand, calling for engagement of greater control and therefore slower, more careful decisions in the face of conflict, and relaxing control and permitting faster, more automatic decisions otherwise. When dysfunctional, persistent signaling from ACC could produce maladaptive perseveration for stimuli that are no longer relevant, the resulting phenotype of which would be compulsive behaviors [5]. Indeed, there is a substantial literature on the role of ACC in the pathophysiology of OCD, as mentioned in Widge et al.

The challenging but tantalizing implication is that we may be on the threshold of an era in which we can target specific neurocognitive domains of psychiatric disorders with a transdiagnostic approach. For example, we may target one region (e.g., ACC ± associated tracts) for cognitive control deficits and another (e.g., orbital or ventral prefrontal cortex) for reward sensitivity deficits, rather than treating all cases of OCD as homogeneous. This approach would be the RDoC (research domain criteria) version of DBS. For now, surgical neuromodulation is likely the best tool we have for this refined approach, as only this modality can possibly target neighboring brain regions and interlacing fiber tracts with the requisite specificity. This specificity is achieved at the expense of invasiveness, but the tradeoff would be worthwhile if risks remain low and outcomes continue to improve.

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AUTHOR CONTRIBUTIONS

SAS and WG wrote this article.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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