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Deep Brain Stimulation: From Sweet Spots to Sweet Networks?

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Tourette syndrome (TS) constitutes a childhood-onset brain disorder with the defining presence of tic behaviors. Tics are repetitive movements or sounds that resemble voluntary actions but appear without embedment to discernable context (1). Effective therapy is complicated by phenotypical heterogeneity, which arises not only from a wide variability of presenting tic behaviors among individuals, but also from commonly co-occurring neuropsychiatric comorbidities—such as obsessive-compulsive behaviors (OCBs), attention-deficit/hyperactivity disorder, anxiety, or depression (1–5). For select, severe cases of TS that are refractory to psychopharmacological or behavioral first-line interventions, deep brain stimulation (DBS) represents a valuable alternative treatment option (1–5) that can reduce tic severity by at least 50% in more than half of patients across proposed targets (2).

While pioneered by Vandewalle *et al.* (6) in 1999 with stimulation to the nucleus ventro-oralis internus and the centromedial-parafascicular thalamic complex, further exploration of this modality as a potential therapy for TS has moved slowly. In particular, owing to variable effectiveness and proportions of nonresponders across several case series, mostly comprising small samples, along with only limited numbers of randomized controlled trials conducted to date, the treatment could not be fully established, nor could a single optimal target be determined among multiple proposed stimulation sites within the cortico-basal ganglia-thalamo-cortical circuit (2,4). Moreover, ambiguities regarding the optimal subterritory within some of these anatomical sites remain [e.g., the posterolateral vs. anteromedial globus pallidus internus (GPi) (2,4)].

In the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Johnson *et al.* (3) zoom into the GPi target zone and apply a sophisticated methodological framework to study localized DBS network effects associated with clinical improvements along the TS symptom spectrum. Based on retrospective, longitudinal multisite data of 35 patients receiving bilateral GPi DBS, the authors first integrated individual electrode locations and stimulation parameters into both single- and bihemispheric activation models for specific normative basal ganglia and internal capsule pathways (7). Comparably higher percentages of stimulation settings activated the associative pallido-subthalamic pathway, ansa lenticularis, and anterior lenticular fasciculus, as well as the premotor and prefrontal internal capsule pathways. Although lateralized stimulation parameters were uncommon among patients, several bundles (most prominently the ansa lenticularis and internal capsule pathways) exhibited asymmetry, possibly owing to hemispheric differences in lead localization.

Second, the resulting bilateral models of estimated pathway activation were related to tic (operationalized via the Yale Global Tic Severity Scale) and comorbid OCB improvements (assessed via the Yale-Brown Obsessive Compulsive Behavior Scale) across patients and stimulation settings. Tic improvement significantly correlated with the relative bilateral degree of activation of the associative pallido-subthalamic tract and ansa lenticularis, as well as the prefrontal internal capsule pathway. OCB improvement, on the other hand, was associated with activation of associative and sensorimotor pallido-subthalamic pathways, along with all three internal capsule pathway partitions.

Finally, recombinations of pathway activation models with multiple patient-wise stimulation parameter settings and clinical variables (months since surgery, baseline severity, and pathway activation) were compared and cross-validated regarding their predictive utility for postoperative tic or comorbid OCB improvements over multiple follow-up time points. The best-fit model for tic outcomes comprised baseline severity combined with bihemispheric associative pallido-subthalamic pathway activation, while the winning model for OCB improvements included baseline severity and bilateral sensorimotor pallido-subthalamic pathway activation. Both models were predictive for symptom-specific outcome across individuals, underscoring their generalizability to novel patients.

In this study, Johnson *et al.* (3) unite numerous strengths that allow for significant conclusions, most notably through an innovative combination of state-of-the-art resources. As one particular highlight, the study's comparably big sample goes against the odds of only handfuls of operations performed on patients with TS at individual centers annually. Doing so was largely enabled by the International TS DBS Registry and Database (4) (https://tourettedeepbrainstimulationregistry.ese.ufhealth.org) initiated by Michael Okun in a combined effort across multiple international DBS sites. This platform is exceptional in its kind, and with aggregation of currently 320 TS DBS cases, it sets an important prototype for data sharing and DBS registries with the potential for efficacious and sufficiently statistically powered research into the effects of DBS for rare, and presently investigational, indications. The article by Johnson *et al*. (3) is a prime example of how much can be achieved if DBS centers collaborate on a global scale.

Apart from that, Johnson *et al.* (3) pave an avenue toward in vivo simulation of white matter pathway activations at particularly granular levels that—if augmented and replicated by future studies—may hold promise for precise planning of stereotactic targeting and postoperative stimulation parameter tuning at the single-subject level. Such fine-grained scale of the anatomical model definition was only possible

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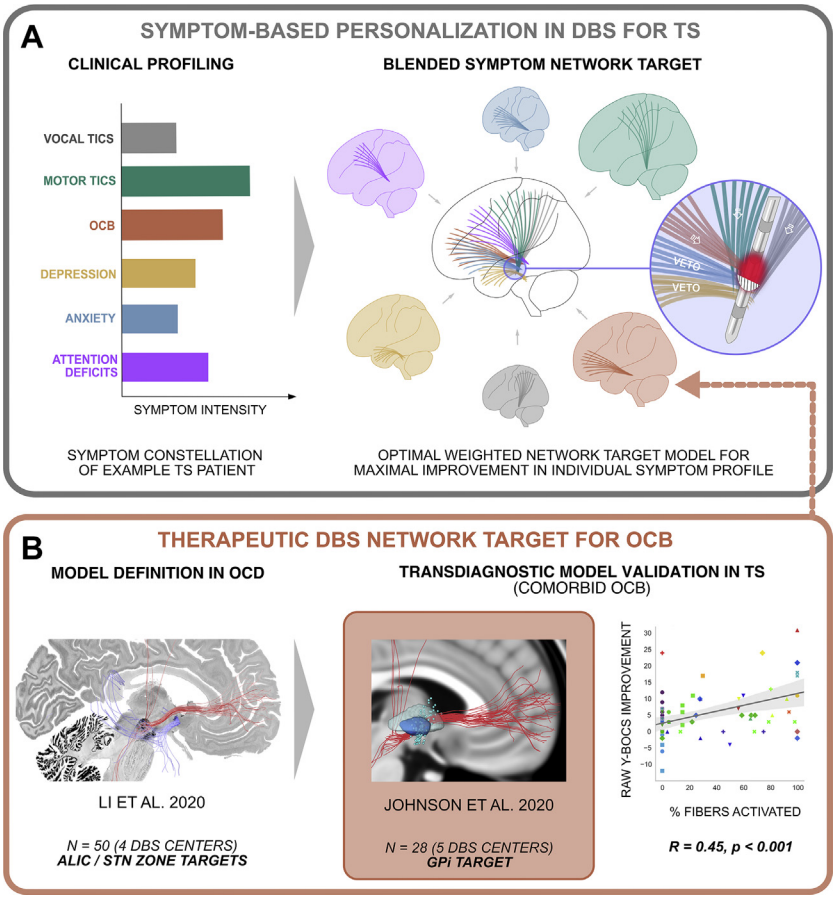

Figure 1. Symptom network blending as a proposed personalization framework for deep brain stimulation (DBS). **(A)** A blend (i.e., a mixture) of symptom network targets, weighted by each respective patient's symptom profile, could inform an optimal stimulation target in the distant future. While this strategy is currently conceptual, the first definitions of symptom-specific networks are emerging. After careful and incremental verification/falsification by future studies, a safe translation to actual patient care could become possible. **(B)** With detailed insights into white matter pathways parcellated by symptom-specific DBS effects, Johnson *et al.* (3) provide an initial groundwork for symptom-tailored brain circuit therapy in patients with Tourette syndrome (TS). Based on the degree of activation of a fiber bundle that had originally been defined as optimal tract target for maximized obsessive-compulsive behavior (OCB) improvements in DBS for obsessive-compulsive disorder (OCD) by Li *et al.* (9), Johnson *et al.* (3) were able to predict outcomes along the same symptom dimension in TS after DBS to the globus pallidus internus (GPi). Importantly, the original tract target had been informed on data of individuals receiving DBS to either anterior limb of the internal capsule (ALIC) or subthalamic nucleus (STN) zone targets, but not to the GPi. However, the identified tract closely passes by the GPi. Such combined evidence across surgical targets and pathologies (3,9) may hint at an optimal transdiagnostic network target effective for treating OCB. Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

using fiber tracts made openly available by the laboratory of Cameron McIntyre in form of a novel holographic basal ganglia pathway atlas (7). Informed by anatomical landmarks from histological and structural magnetic resonance imaging data along with estimated pathway trajectories in a first-of-its-kind 3-dimensional visualization environment, tract courses were manually curated by some of the world expert neuroanatomists of the basal ganglia (Suzanne Haber, Martin Parent, Yoland Smith, and Peter Strick). As such, this normative atlas resource provides substantial anatomical accuracy of the subthalamic region and bypasses the limitations of diffusion-weighted imaging–based tractography (7). In our view, DBS research owes a great deal of its success to such milestones and steady advancements in modern neuroimaging or bioinformatic methodology, which are capable of tracing the propagation of DBS-induced axonal activation throughout the connectome in increasingly precise and pathophysiologically truthful fashion (7,8).

Johnson *et al.* (3) build upon previous work by the same group identifying structural connectivity activated by DBS as major predictors for improvements in tic severity (5). While the first study applied normative whole-brain connectomes, involved both pallidal and thalamic targets, and adopted a "broader lens view" of whole-brain scale modeling, the present study focuses on details surrounding the pallidal target. Both studies are embedded within the emerging field of connectomic DBS, which endorses an important paradigm shift from understanding stimulation impact at the local target level toward distributed DBS network effects (8). Instead of elucidating one most optimal, focal target coordinate (or sweet spot), this conceptual transition has incited investigations into sweet networks that could be activated via stimulation to multiple—similarly optimal—entry points, each associated with maximal clinical improvements (8–10).

This relatively young field of neuroimaging research integrates with a longstanding tradition of functional neurosurgery that aims to treat pathologies as specific disruptions emerging within the wiring diagram of the human connectome (hence the term circuitopathies). As early as in 1890, neurosurgical lesioning had been performed with the intention of interrupting pathological information flow between neuronal subsystems or nodes by separating them (8). More deliberated evolutions of this concept may be seen in the form of capsulotomies as pioneered by Jean Talairach and Lars Leksell in the 1950s, from which the present concept of DBS to the anterior limb of the internal capsule originated (8). Similarly, early treatment attempts for TS via thalamic DBS surgery (6) took inspiration from thalamotomies, as advanced by Rolf Hassler in 1970 (4), with probable far-fetching consequences for white matter tracts linking to this widely connected structure. Johnson *et al.* (3,5)

add to the idea that therapeutic TS DBS may rely on stimulation effects onto the complex interplay between limbic, associative, and motor dysfunctions in cortico-basal ganglia-thalamo-cortical loops underlying TS symptomatology (1).

One highly intriguing secondary finding of their study (3) might be seen in its differential mechanistic insights that allow disentangling of pathway-specific contributions of DBS to tic versus comorbid OCB improvements. It has been proposed that variability in outcomes across DBS targets and stimulation parameters may be related to which symptoms surgical planning and stimulation protocols have been optimized for (e.g., tics and/or comorbidities) (8). In this respect, behaviorally selective DBS networks as established by Johnson *et al.* (3) could help unify brain circuit therapy across studies to some degree and achieve personalization to patient-wide phenotypical heterogeneity. Specifically, addressing nonuniform clinical presentations via a single fixed implantation site, deemed effective on the group level, may neglect differential network effects related to individual symptom and comorbidity constellations. Instead, patient-tailored DBS strategies will likely require modulating unique blends of symptom-specific—rather than disease-specific—circuits (Figure 1A) (8).

Relatedly, network-informed dimensional symptom conceptions, as proposed within the scope of the Research Domain Criteria initiative of the U.S. National Institute of Mental Health (https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/), have supported the idea that TS could align with other pathologies—such as obsessive-compulsive or addictive disorders—along a shared compulsivity dimension. Indeed, Johnson *et al.* (3) were able to explain variance in OCB outcomes in their sample based on the degree of activation of a fiber bundle that had originally been defined as an optimal target for maximized OCB improvements in obsessive-compulsive disorder (9). Crucially, this tract had been calculated on data of patients receiving DBS to the subthalamic nucleus or anterior limb of the internal capsule zones, but not to the GPi. The fact that, independently of three target sites and two disorders, stimulation to the same white matter bundle was predictive of OCB outcome may point toward a therapeutic compulsivity network (Figure 1B) (3,9,10). Building on careful symptom-specific network parcellations as those described by Johnson *et al.* (3), we anticipate an increasing independence from disease-centricity to push personalized neuromodulation forward based on pathophysiological meaningfulness and transdiagnostic knowledge transfer.

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