Biological Psychiatry

Review

Connectomic Deep Brain Stimulation for Obsessive-Compulsive Disorder

Juan Carlos Baldermann, Thomas Schüller, Sina Kohl, Valerie Voon, Ningfei Li, Barbara Hollunder, Martijn Figee, Suzanne N. Haber, Sameer A. Sheth, Philip E. Mosley, Daniel Huys, Kara A. Johnson, Christopher Butson, Linda Ackermans, Tim Bouwens van der Vlis, Albert F.G. Leentjens, Michael Barbe, Veerle Visser-Vandewalle, Jens Kuhn, and Andreas Horn

ABSTRACT

Obsessive-compulsive disorder is among the most disabling psychiatric disorders. Although deep brain stimulation is considered an effective treatment, its use in clinical practice is not fully established. This is, at least in part, due to ambiguity about the best suited target and insufficient knowledge about underlying mechanisms. Recent advances suggest that changes in broader brain networks are responsible for improvement of obsessions and compulsions, rather than local impact at the stimulation site. These findings were fueled by innovative methodological approaches using brain connectivity analyses in combination with neuromodulatory interventions. Such a connectomic approach for neuromodulation constitutes an integrative account that aims to characterize optimal target networks. In this critical review, we integrate findings from connectomic studies and deep brain stimulation interventions to characterize a neural network presumably effective in reducing obsessions and compulsions. To this end, we scrutinize methodologies and seemingly conflicting findings with the aim to merge observations to identify common and diverse pathways for treating obsessive-compulsive disorder. Ultimately, we propose a unified network that—when modulated by means of cortical or subcortical interventions—alleviates obsessive-compulsive symptoms.

https://doi.org/10.1016/j.biopsych.2021.07.010

Deep brain stimulation (DBS) for obsessive-compulsive disorder (OCD) can be an effective treatment for severely affected and treatment-refractory cases (1–3) but is still not considered a fully established therapy (4). This is at least in part due to uncertainty about the precise brain networks to modulate for optimal treatment response. The anatomical and functional characterization of circuits that, when stimulated, reduce obsessions and compulsions could improve the risk-benefit profile of DBS and provide testable hypotheses for neuromodulation of OCD in general.

Remarkably, different DBS targets have shown comparable response rates in OCD (5,6). Previous work demonstrating that DBS exerts clinical effects beyond the local/focal stimulation target (7,8) has motivated the concept of a broader, potentially shared neural network responsible for improvement of obsessions and compulsions. In parallel, OCD is a heterogeneous disorder, with evidence suggesting that a varying set of multiple networks may be affected in each patient, and thus relevant for neuromodulatory treatment (9). Connectomic DBS is a rapidly developing neuroscientific concept that can help to understand how different target regions contribute to clinical improvement via linked networks. In this critical review, we aim to scrutinize methodologies and findings from connectomic studies and DBS interventions for OCD to identify common and diverse pathways likely to be effective for reducing obsessions and compulsions. We focus on structural connectivity for the sake of conciseness; relevant functional magnetic resonance imaging (MRI) studies in OCD DBS (7,10–12) are discussed where appropriate.

FROM FOCAL TARGETS TO INTERCONNECTED NETWORKS

The idea of modulating a network (instead of a focal brain region) with surgery is not new. Around 1950, Jean Talairach and Lars Leksell independently began lesioning the anterior limb of the internal capsule (ALIC), with the aim of disrupting a network between limbic and prefrontal regions (13). In particular, patients with OCD improved after ablations of the ALIC (capsulotomy) or the anterior cingulum (cingulotomy) (14,15). Following this work, the first target used for DBS in OCD was the ventral ALIC (16,17). In the following years, different nuclei adjacent to the ALIC, including the ventral striatum (VS) containing the nucleus accumbens (NAc) as well as the bed nucleus of the stria terminalis (BNST), have been proposed as key regions for successful DBS (18,19). Through empirical evidence from DBS in movement disorders, other brain targets such as the subthalamic nucleus (STN), the inferior thalamic

ISSN: 0006-3223

peduncle, and the superolateral branch of the medial forebrain bundle (MFB) [later referred to as ventral tegmental area (VTA) projection pathway (20) or midbrain target (21)] have been successfully targeted in OCD (3,22,23). Remarkably, modulation of these distinct subcortical targets (Figure 1) all show the potential to improve obsessions and compulsions, pointing toward a common network responsible for clinical efficacy. Using modern MRI technology such as diffusion-weighted imaging based tractography (diffusion MRI [dMRI]), we are now poised to create realistic in silico models of how these different sites of intervention may form nodes that assemble a common network (Figure 2). Specifically, by mapping clinical effects onto modulated neural pathways, researchers have begun to identify connectivity profiles associated with clinical efficacy (24). Undeniably, classic analysis of optimal spots can further complement such network analysis to characterize or validate specific hubs (i.e., for surgical targeting) within a given network. Box S1 outlines different methodological approaches that have been used in OCD DBS so far (see Supplement for a more detailed discussion).

CONNECTOMIC STUDIES OF DBS FOR OCD

In a first connectomic approach toward DBS for OCD, Hartmann *et al.* (25) investigated 6 patients who underwent ALIC/NAc-DBS employing tract activation modeling using a normative dMRI brain atlas (Approach A in Box S1). In 2 responding patients, stimulation particularly affected fibers reaching the right anterior middle frontal gyrus/dorsolateral prefrontal cortex (dlPFC), while nonresponders stimulated the lateral orbitofrontal cortex (OFC). The authors concluded that targeting right dlPFC fibers leads to optimal response, while negative outcomes resulted from widespread activation of nontherapeutically relevant fibers. While the latter conclusion (i.e., negative outcome associated with widespread activation) was not directly replicated in further studies discussed below, the study also suggested that modulation of a more centrally rather than ventrally located white matter pathway within the ALIC was associated with optimal treatment response (25).

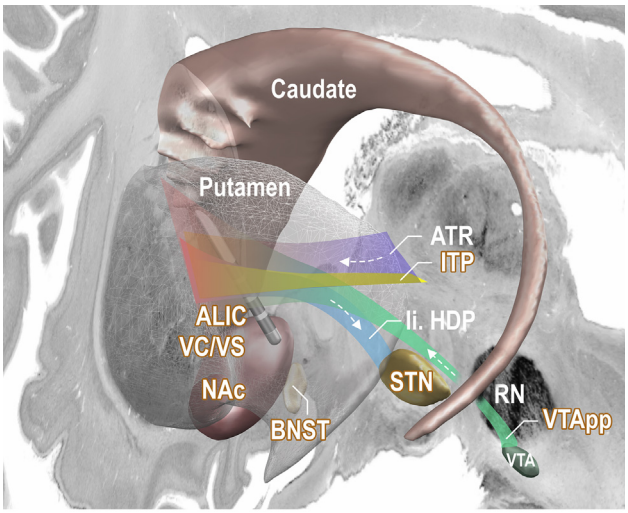

Figure 1. Different surgical deep brain stimulation concepts for obsessive-compulsive disorder and surrounding structures. Tracts traversing the anterior limb of the internal capsule (ALIC) (anterior thalamic radiation [ATR]; limbic/associative hyperdirect pathway [li. HDP]) have been added schematically. Structures that have been targeted by deep brain stimulation are outlined in orange. Please note that the aim of the figure is to outline surgical concepts that have been proposed in the literature. As discussed in this review, some are built on conflicting theories and thus may not be necessarily anatomically/mechanistically plausible. Left panels show inset relative to the whole brain for orientation on the T1 Montreal Neurological Institute 2009b (8) and BigBrain (9) templates. BNST, bed nucleus of the stria terminalis; ITP, inferior thalamic peduncle; NAc, nucleus accumbens; RN, red nucleus; VC/VS, ventral capsule/ventral striatum; VTApp, ventral tegmental area projection pathway (formerly superolateral branch of the medial forebrain bundle); STN, subthalamic nucleus.

Liebrand *et al.* (26) investigated 12 patients with ALIC/NAc-DBS using individual preoperative dMRI and calculated the distance of active electrode contacts to specific fibertracts, the anterior thalamic radiation, and the superolateral branch of the MFB (Approach B in Box S1). Both fiber bundles were reconstructed using probabilistic tractography with the anterior thalamic nucleus or the VTA as seed regions, respectively, and the ventral ALIC as waypoint based on previous studies (27). The authors observed a significant positive correlation between clinical improvements and the proximity ratio in favor of the MFB compared with the anterior thalamic radiation. We note that the nomenclature and conceptualization of this fiber tract identified as MFB has since evolved (21) and that the original authors now refer to this structure as VTA projection pathway (20), while others referred to it as a midbrain projection (21) (see below for a detailed discussion).

Using a different methodological approach (Approach C1 in Box S1), Baldermann *et al.* investigated a cohort of 22 subjects who underwent ALIC/NAc-DBS (28). Optimal voxelwise structural connectivity profiles were calculated based on individual dMRI data in one group and based on normative dMRI data in another. The resulting maps constituted models of optimal connectivity capable to explain significant amounts of variance in outcomes in patients of the other subsample, indirectly highlighting the utility of both individual and normative dMRI for connectomic DBS. A final model of optimal connectivity using the normative connectome data across the whole group revealed that connectivity between stimulation sites and both lateral and medial prefrontal cortices could be cross-validated with significant correlations in a leave-one-patient-out design. Finally, a fiber-centric analysis (Approach C2 in Box S1) was introduced to further determine the subcortical representations of this beneficial connectivity profile. This analysis revealed a fiber bundle that connected the lateral and medial prefrontal cortex with the thalamus and STN, which traversed the ALIC centrally.

Further developing this novel approach (C2)—which has since been termed DBS fiber filtering or discriminative tractography—Li *et al.* published the largest study (N = 50) to date to determine connectivity associated with response to DBS for OCD (29). First, the same sample employed in the Baldermann *et al.* study (28) was included (ALIC/NAc target). Second, a cohort of 14 subjects who received DBS of the STN was added. Results were validated by calculating the tract model on the first cohort and overlaying stimulation volumes of the second cohort with it to generate coefficients termed fiber T scores. High scores would suggest optimal clinical outcomes, while low scores would suggest poor clinical

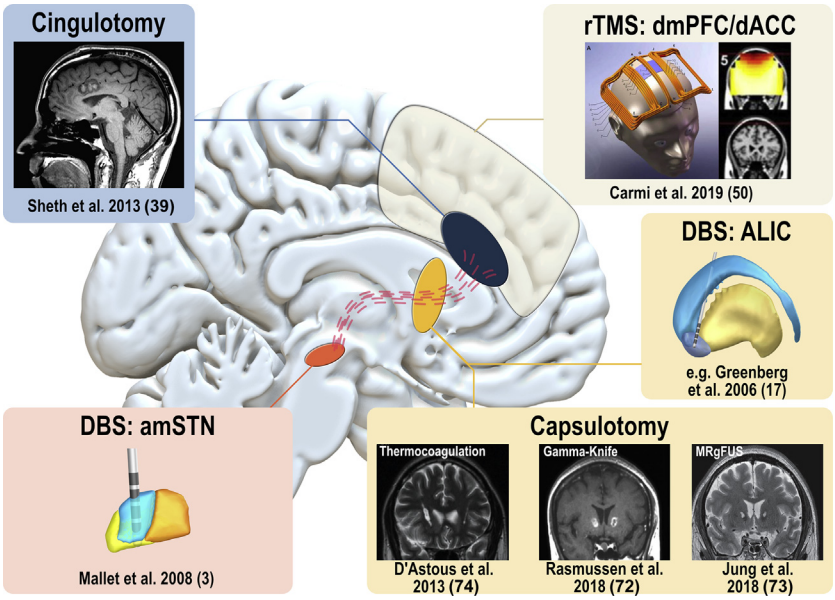

Figure 2. Effective neuromodulative treatments for obsessive-compulsive disorder (OCD) with schematic display of target regions. Existing target regions may give additional clues about a common pathway for treating OCD. Currently, the U.S. Food and Drug Administration approves 2 interventions: An H-coil transcranial magnetic stimulation (TMS) system targets the dorsal anterior cingulate cortex (dACC) and dorsomedial prefrontal cortex (dmPFC) (50) and deep brain stimulation (DBS) of the anterior limb of the internal capsule (ALIC) (17). Another target for DBS, the anteriomedial subthalamic nucleus (amSTN), showed efficacy in patients with OCD in a randomized controlled clinical trial (3). Meta-analysis of observational studies involving capsulotomy (72–74) and cingulotomy (41) show efficacy in severe OCD as a last-resort treatment, although controlled studies are lacking. MRgFUS, magnetic resonance-guided focused ultrasound; rTMS, repetitive TMS. All panels reproduced, with permission, from original work. Panel rTMS reproduced from (75). Panel by Jung 2017 distributed under the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0).

outcomes. The calculated scores significantly correlated with clinical improvements in both directions, i.e., after calculating the tract model on the first to explain variance in the second cohort, and vice versa. Finally, two smaller samples from independent centers [N = 8 targeting the NAc and N = 6 targeting the ALIC/NAc region and STN in a crossover trial (30)] were used to validate results. By doing so, the hypothesized pathway for OCD DBS was refined, showing again that streamlines connecting the lateral and medial prefrontal cortex with the anteromedial STN and medial dorsal nucleus of the thalamus were associated with successful DBS. A more conservative analysis of the data using a tractography atlas of basal ganglia pathways (31) (which is less prone to false positives) confirmed a fiber bundle connecting the dorsal anterior cingulate cortex (dACC) with the STN via the ALIC as the strongest candidate tract represented by the atlas. After consultation with 4 anatomists, the tract was classified to represent a central subsection of the ALIC that involves hyperdirect input to the nonmotor STN.

The resulting tractographic profile (29) was made publicly available as a reference for scientific use (Figure 3, top right). An independent research group confirmed the predictive value of the pathway in 10 subjects with OCD and DBS of the ALIC/VS applying the same analysis procedure (32). A second group recalculated an optimal tract using the same methodology on a novel sample of 8 patients and identified the same bundle in direct comparison to the published one (33). The significant association between clinical improvement and the extent of modulating this specific pathway was reproduced in both studies (32,33).

Another recent report applied connectomics to study a cohort of 9 patients with OCD undergoing DBS targeting the BNST (1). In a voxel-by-voxel analysis, structural connectivity to the right ventrolateral PFC (vlPFC) and hippocampal regions and also to parietal and dorsomedial prefrontal areas significantly explained variance of response to DBS. A complementary fiber filtering analysis revealed, among others, white matter fibers within the ALIC that connected the stimulation site to the midbrain, traversing the BNST onward to the right vlPFC. This tract again graphically matched the pathway identified by Li *et al.* (29) (with a slightly more ventral course and overlap with the originally published tract) and correlated positively with clinical outcomes to a similar degree—albeit not significantly (Figure 3). Lastly, a recent investigation of 28 patients with Tourette syndrome treated with DBS of the anterior globus pallidus internus showed that modulation of the pathway published by Li *et al.* (29) was a significant predictor of improvement in obsessive and compulsive symptoms in these patients (34). This observation is remarkable because it suggests that DBS for OCD might act via symptom-specific rather than disease-specific networks. Specifically, it shows first evidence that the same network modulation approach could be effective transdiagnostically (a narrative that complies with the longstanding idea to study brain functions instead of nosological entities). Figure 3 summarizes the initial findings (28,29) and confirmatory results (1,8,33,34).

It is important to note that some of the quoted studies also highlighted additional relevant pathways, i.e., located directly dorsally (32) or ventrally (1) to the tract published by Li *et al.* (29) or connections between the amygdala and the BNST (1). As the respective authors rightly stated (32), a putative network associated with DBS response in OCD is likely not restricted to the already identified pathway but rather involves further connections yet to be uncovered, which is discussed in the later section, Further Pathways and Factors Relevant for Neuromodulation in OCD. Along with studies involving structural connectomics, there is also a growing body of literature on changes in metabolic, functional, or electrophysiological activity in the brain during DBS for OCD. An oxygen-15 positron emission tomography study by Dougherty *et al.* revealed

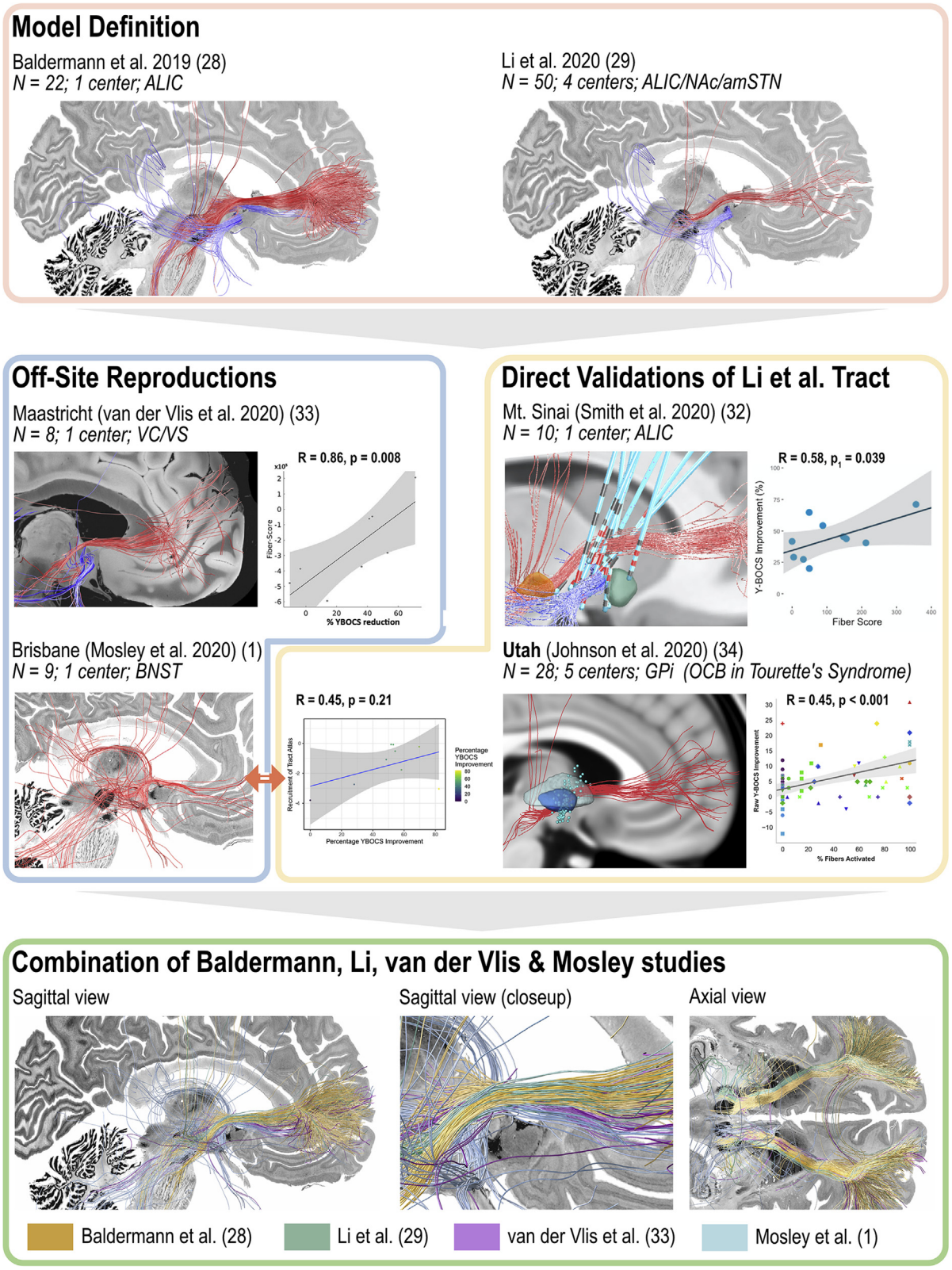

Figure 3. Summary of findings reported in Baldermann *et al.* (28) and Li *et al.* (29) (top) as well as off-site confirmations from additional studies (bottom). Modulating red fibers was associated with optimal improvements, while modulating blue fibers associated with poor response along the Yale-Brown

an acute perfusion increase within the dACC and basal ganglia during ventral ALIC/NAc stimulation, which correlated with improvement of affective symptoms (35), while Suetens *et al.* reported a decreased metabolism with active DBS in the ACC and inferior, middle, and frontal gyri (36). In this study, capsulotomy for OCD resulted in an analog reduction in metabolic activity in the ACC. Figee *et al.* reported a DBS-induced reduction in hyperconnectivity with the ACC and lateral prefrontal cortex seeding from the NAc, which was associated with greater reduction of obsessions and compulsions (7). A later study performed a region of interest–based analysis of directional functional connectivity, showing that active DBS increased the impact of the ventromedial PFC (vmPFC) on an amygdala-insula network along with improvements in depression and anxiety symptoms (10). Moreover, there is a number of electrophysiological studies showing that active DBS of the ALIC/NAc interferes with low frequency oscillations within the mPFC/ACC, which can be linked to improvements in obsessions and compulsions (7,8,37) and cognitive performance during conflicts (here, DBS increased theta power in mPFC and vlPFC in patients with OCD and depression) (38). The role of ACC-mediated cognitive performance during conflict in neuromodulation for OCD is further supported by data from patients undergoing cingulotomy (39–41). Taken together, these studies represent further evidence for the involvement of a central pathway encompassing the ACC and vlPFC in DBS for OCD beyond structural connectomics. Still, they also show that further circuits, especially involving the vmPFC, likely play a role in DBS for OCD. In summary, connectomic studies for OCD DBS provide growing evidence that a specific pathway within the ALIC carries out reductions in obsessions and compulsions, which is in part supported by studies using different modalities (functional MRI, positron emission tomography, electrophysiology). As outlined below, studies using different stimulation sites (ALIC, NAc, STN) are for the most part congruent in that modulation of fibers from the medial and lateral PFC, centrally traversing the ALIC and connecting the STN and thalamus, accounts for positive outcomes of OCD DBS.

ANATOMICAL CONSIDERATIONS

While some of the aforementioned studies agreed on the critical role of the same fiber bundle published as a three-dimensional dataset (1,28,29,32–34), others revealed seeming heterogeneity about which pathway would be critical to modulate for successful DBS in OCD. Namely, the study by Liebrand *et al.* suggested that the MFB, connecting the PFC with the VTA, would be associated with a beneficial response (26), whereas other studies highlighted streamlines within the ALIC as being critical for OCD DBS (28,32,42). Conventionally, the MFB is a transhypothalamic structure that does not traverse the ALIC (20,21)—and seen in this light, the studies would imply a conflicting finding. Reviewing the respective literature more in depth, however, suggests that this apparent discrepancy is in fact a matter of nomenclature. The fiber tract defined by Liebrand *et al.* (26) labeled as MFB was reconstructed using dMRI by placing a waypoint seed into the ALIC. This resulted in a bundle that passed the ALIC considerably dorsally to the NAc (Figure 4). The group was relying on former work by Coenen *et al.*, who conceptualized the tract based on dMRI tractography (referred to as superolateral branch of the MFB) as a potential target for treating depression (27,43). However, anatomy textbooks of the human brain (44), histological atlases (45,46), and a recent anatomical review of brain regions relevant for OCD DBS (21) confirm that the MFB is not part of the internal capsule (Figure 4). Thus, the streamlines referred to as superolateral MFB instead represent fibers of the internal capsule. Of note, there is uncertainty whether the functionally relevant connections are the ones from the VTA projecting through the internal capsule to the PFC and/or descending PFC-brainstem connections that send axon collaterals to regions such as the STN and VTA (21). Thus, a more appropriate description of the pathway described by Liebrand *et al.* (26) could indeed be a cortico-midbrain projection traversing within the ALIC. These insights harmonize aforementioned findings with reports of the superolateral MFB/midbrain target/VTA projection pathway as an effective target for OCD (23), which, by its shape, again represents the same bundle (47).

Assembling all evidence, multiple studies from differing research groups with differing patient samples and targets converge on a highly similar effective stimulation site within the ALIC (Figure 5)—although authors had used different pathophysiological concepts to explain results (Figures 1 and 4). Evidence from nonhuman primate tract tracing suggests that this spot may best be described by the central portion of the ALIC with projections from the dACC and vlPFC (21,48). The hyperdirect pathway projecting from the dACC to STN was the most predictive tract from a set of anatomically predefined pathways in the $N = 50$ study by Li *et al.* (29). In a recent report, the same patients studied by Li *et al.* were reexamined based on functional connectivity, which has the advantage to include indirect connections. Again, a common network attributed a central role to the dACC (12). Further support for the dACC as a strong cortical candidate region is provided by the efficacy of anterior cingulotomies in treating OCD (Figure 2) (49). Furthermore, a Food and Drug Administration–approved H-coil

Obsessive Compulsive Scale score in respective studies. While some studies applied the published dataset from the Li *et al.* study to test how much variance in clinical outcomes it could explain in their sample (yellow box), others calculated a novel tract using the same method and graphically compared results [van der Vlis *et al.* (33)] or did both [(Mosley *et al.* (1)]. Note that the study by Johnson *et al.* (34) investigated patients with Tourette syndrome and comorbid obsessive-compulsive behavior (equally measured by the Yale-Brown Obsessive Compulsive Scale score). The green box shows a direct overlap of results from the studies by Baldermann *et al.* (28), Li *et al.* (29), and Mosley *et al.* (1), respectively. In direct synopsis, the tract calculated by Mosley *et al.* traversed more ventrally. However, when overlaying their volumes of activated tissue with the tract calculated by Li *et al.*, this was positively associated with clinical improvement (albeit not significantly). ALIC, anterior limb of the internal capsule; amSTN, anteromedial subthalamic nucleus; BNST, bed nucleus of the stria terminalis; GPi, globus pallidus internus; NAc, nucleus accumbens; OCB, obsessive-compulsive behavior; VC/VS, ventral capsule/ventral striatum. Panel by Smith *et al.* (32) reproduced, with permissions, from the original publication (other panels show original content).

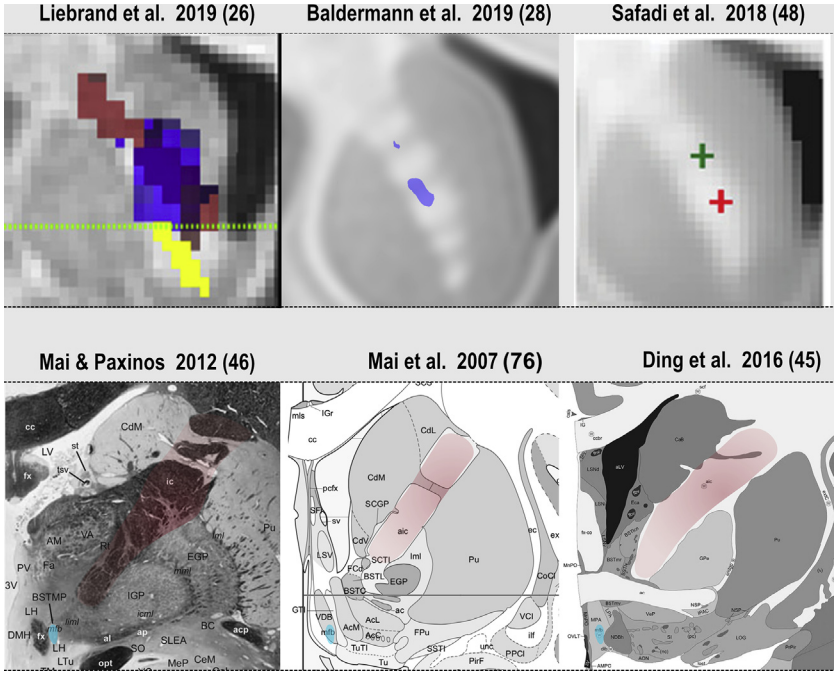

Figure 4. Differences in anatomical nomenclature have led to confusion in the deep brain stimulation for obsessive-compulsive disorder literature. Top: optimal tract targets mediating deep brain stimulation treatment by Liebrand *et al.* (26) and Baldermann *et al.* (28) are marked in blue. The former was termed medial forebrain bundle, while the latter was termed frontothalamic radiation/anterior limb of the internal capsule (ALIC). Based on anatomical tracer data in macaques (21), this site within the central ALIC best conforms to projections from the dorsal anterior cingulate cortex and ventrolateral prefrontal cortex (right). Bottom: classical definition of the medial forebrain bundle (cyan) in coronal sections from three anatomical reference atlases (45,46,76) compared with the ALIC (red). According to these atlases, the medial forebrain bundle takes a transhypothalamic route and is not part of the ALIC. Panel by Liebrand *et al.* reproduced with permissions from Liebrand *et al.* (26). Panel by Safadi *et al.* (48) reproduced under the Creative Commons Attribution 4.0 International License. Panel from Ding *et al.* (45) retrieved from https://www.brain-map.org. Figure panel Mai & Paxinos reproduced, with permission, from Mai and Paxinos (46). Figure panel Mai *et al.* reproduced, with permission, from Mai *et al.* (76).

transcranial magnetic stimulation system targets the dACC and medial prefrontal cortex (50). Other DBS studies have also reported the importance of the vlPFC (1,29) and middle frontal gyrus/dlPFC (25,28). As shown in Figure 5, white matter tracts from the PFC/ACC travel through the ALIC in a topologically organized manner. By nature, dMRI-based tractography may not be able to distinguish these cortical representations with certainty. Subcortically, the connectomic evidence so far highlights the pivotal role of the anteromedial STN and the thalamus (29).

A MECHANISTIC MODEL OF CONNECTOMIC NEUROMODULATION FOR OCD

Based on the evidence of connectomic DBS for OCD reviewed above, we propose a novel network model for an underlying mechanism of neuromodulation for OCD. Data indicate a central role for the dACC and that modulation of a hyperdirect connection of medial and lateral prefrontal cortices to the STN is associated with DBS response. Thus, the STN as an entry point for cortical information in terms of a hyperdirect pathway appears to be relevant for treatment of OCD, apart from the commonly accepted dysfunctional frontostriatal input related to the direct and indirect pathway (51,52). Secondly, projections between the anterior thalamus and PFC seem important (Figure 6). Considering the topological configuration of white matter tracts in the ALIC, the pathway can be described as a central ALIC pathway. Precise origination and termination points of this pathway remain unclear. However, some clues exist. As outlined, the dACC is a strong candidate derived from tractographic studies and is in line with alternative effective neuromodulation strategies for OCD, i.e., cingulotomy and transcranial magnetic stimulation, but methodological limitations prevent a definite conclusion regarding other cortical areas (i.e., vlPFC, dlPFC, and vmPFC) that may be involved (Table 1).

Crucially, modulation of this circuit could take place at different nodes of the network: first, via DBS to the ALIC, STN, thalamus, and, potentially, globus pallidus internus; second, via ablative neurosurgery to dACC and ALIC; and third, via transcranial magnetic stimulation of the dACC. Importantly, the different targets within this loop are not necessarily interchangeable. Indeed, the fact that different targets are equally capable of modulating this specific network makes it even more important to understand what surmounting differences exist between them. For instance, a clinical trial including both the ALIC/NAc and STN targets in the same patients revealed different structural connectivity of these targets, although clinical improvement of obsessive-compulsive symptoms of both targets could be assigned to the same pathway (30). This suggests that each target additionally modulated different brain networks and, possibly, functions. Indeed, the authors distinguished that while ALIC/NAc-DBS had a greater effect on comorbid depression, STN DBS was associated with improved cognitive flexibility.

Finally, the concept of a common network for improving OCD symptoms may be independent of the disorder. As outlined, comorbid obsessions and compulsions in patients with Tourette syndrome improved when the central ALIC pathway was stimulated (34) (Figure 3). Thus, the proposed network may be effective in improving obsessions and compulsions, rather than OCD (as a categorical disease). Importantly, OCD is a highly heterogeneous disorder. Apart from specific OCD subtypes, e.g., washing, checking, and so on, the putative underlying neuropsychological mechanisms are also

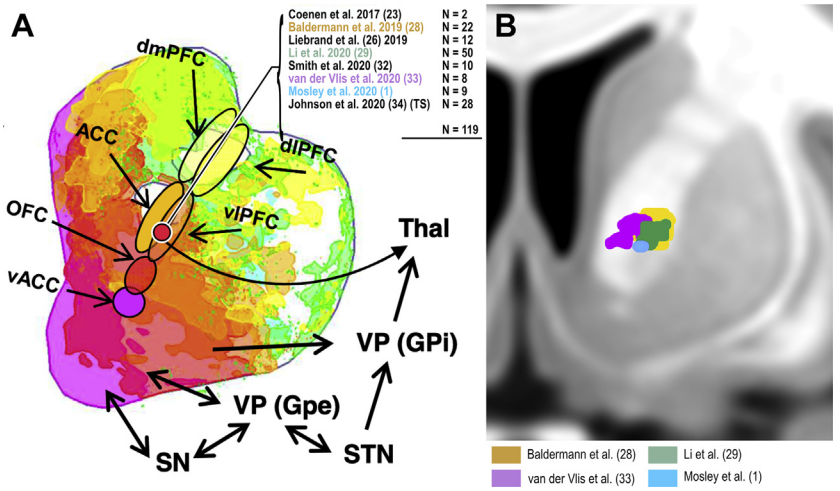

Figure 5. Synopsis of anatomical organization of the anterior limb of the internal capsule with tractography results of obsessive-compulsive disorder deep brain stimulation studies. **(A)** Anatomical organization of the anterior limb of the internal capsule as reported by Haber *et al.* (21). A central part of the anterior limb of the internal capsule has been used by most if not all studies investigating the matter (see list). Note that the *N* = 22 patients from Baldermann *et al.* (28) were used in Li *et al.* (29) as well and hence were only counted once when calculating the sum of 119 patients across studies. Note that the cohort reported by Johnson *et al.* (34) comprised patients with Tourette syndrome with comorbid obsessive-compulsive symptoms. **(B)** Synopsis of studies from Baldermann *et al.*, Li *et al.*, van der Vlis *et al.* (33), and Mosley *et al.* (1) that converge on a similar region. The same data as in Figure 3 are shown in a coronal cross section at y = 8 mm overlaid on top of the ICBM2009b nonlinear asymmetric Montreal Neurological Institute template. Tracts were converted from streamlines to volumetric (tract-density) form using Lead-DBS and visualized using MRIcroGL (NITRC; University of Massachusetts Medical School, Worcester, MA) software. ACC, anterior cingulate cortex; dlPFC, dorsolateral PFC; dmPFC, dorsomedial PFC; Gpe, globus pallidus externus; GPi, globus pallidus internus; OFC, orbitofrontal cortex; PFC, prefrontal cortex; SN, substantia nigra; STN, subthalamic nucleus; Thal, thalamus; vACC, ventral ACC; vlPFC, ventrolateral PFC; VP, ventral pallidum. Figure adapted, with permission, from Haber *et al.* (21).

widespread, e.g., impaired habit versus goal-directed behavior, cognitive inflexibility, emotional vulnerability, or altered risk evaluation. These underpinning principles may in turn serve as transdiagnostic dimensions for other compulsivity-related disorders, such as behavioral addiction, substance use disorders, Tourette syndrome, and autism-related stereotypies (51,53). Thus, a next step toward a more effective and personalized neuromodulation for OCD will be to characterize these endophenotypes and identify through which networks each may be effectively modulated (9).

This framework adds important insights to the prevailing network models for OCD. Based on ground-breaking animal studies that proved the critical role of the OFC for compulsive symptoms (54,55), researchers have often focused on the role of orbitofronto-striatal dysfunctions to explain clinical effects of DBS (56). To date, we understand OCD as a multiple circuit disorder in which each pathway contributes to different aspects of the disease (9,52,57). In line with this notion, connectomic studies for OCD DBS provide evidence that modulating specific circuits relevant in OCD pathophysiology (i.e., a central ACC-ALIC-STN pathway and possibly a vmPFC-related pathway) can lead to clinical improvement. Furthermore, our review highlights the potential role of the STN in OCD therapy as an entry point for cortical information from the PFC in terms of a hyperdirect pathway.

FURTHER PATHWAYS AND FACTORS RELEVANT FOR NEUROMODULATION IN OCD

We must reiterate that this proposed mechanistic model forms one possible mechanism of action—and could represent part of a larger network. Modulation of additional loops (e.g., ventral and dorsal frontostriatal loops, fronto-midbrain connections) and respective changes in symptom

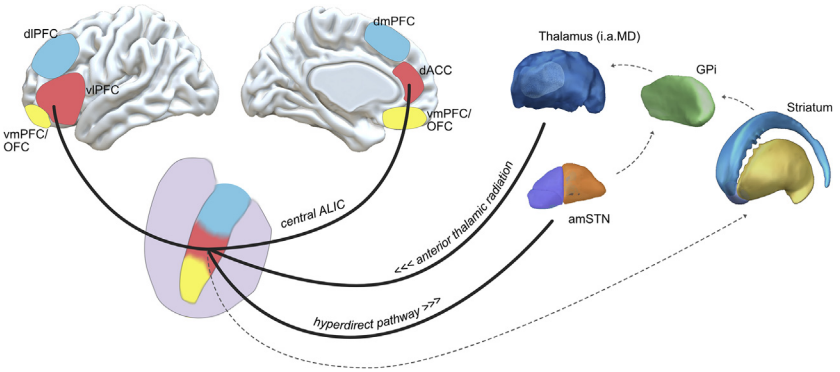

Figure 6. A proposed mechanism of action for connectomic neuromodulation in obsessive-compulsive disorder. Displayed are areas implicated in the pathophysiology of obsessive-compulsive disorder (upper right) and their representation within the anterior limb of the internal capsule (ALIC) (bottom left). The right panel schematically illustrates connections with the basal ganglia. Solid arrows represent evidence from connectomic studies so far: effective deep brain stimulation is associated with fibers from the medial (dorsal anterior cingulate cortex [dACC]) and ventrolateral prefrontal cortex (vlPFC) that traverse the ALIC centrally. Subcortically, these fibers connect with the anteromedial subthalamic nucleus (amSTN), representing a hyperdirect pathway. In addition, modulating fibers from the thalamus (inter alia the medial dorsal nucleus, medial dorsal [MD]) to the PFC along the ALIC (not illustrated) seem to contribute to clinical outcome. Additional loops that may contribute to beneficial effects of deep brain stimulation for obsessive-compulsive disorder include a ventral loop from the ventromedial PFC (vmPFC) and orbitofrontal cortex (OFC), connecting with the ventral striatum and a dorsal loop involving the dorsolateral PFC (dlPFC) and dorsomedial PFC (dmPFC). GPi, globus pallidus internus.

Table 1. Structural Connectomic Studies of DBS for Obsessive-Compulsive Symptoms

Study	*N*	Indication	Target	Connectivity Estimate	Methodology	Beneficial Connectivity		
						Cortical Representation	Subcortical Representation	Pathway Specification
Hartmann *et al.* (25)	6	OCD	ALIC/NAc	Normative structural connectivity	Pathway-activation models	Right MFG/dlPFC		ALIC
Baldermann *et al.* (28)	22	OCD	ALIC/NAc	Individual and normative structural connectivity	DBS network modeling, Fiber filtering	Medial and lateral PFC	Thalamus, nucleus subthalamicus, BNST	FTR/ALIC
Liebrand *et al.* (26)	12	OCD	ALIC/NAc	Individual structural connectivity	Spatial pathway dependency	PFC	Ventral tegmental area	VTApp/Midbrain pp
Li *et al.* (29)	50	OCD	ALIC/NAc, STN	Normative structural connectivity	Fiber filtering	dACC, vlPFC	amSTN, MD	ALIC
Mosley *et al.* (1)	9	OCD	BNST	Normative structural connectivity	DBS network modeling, Fiber filtering	Right vlPFC	BNST, amygdala, circuit of Papez	ALIC
Smith *et al.* (32)	10	OCD	ALIC/NAc	Normative structural connectivity	Fiber filtering	Validation of the pathway identified in Li *et al.* (29)		
Johnson *et al.* (34)	28	GTS	GPi	Normative structural connectivity	Pathway-activation models	Associative/sensorimotor pallido-subthalamic pathway and internal capsule Validation of the pathway identified in Li *et al.* (29)		
Van der Vlis *et al.* (33)	8	OCD	VC/VS	Normative structural connectivity	Fiber filtering	Medial and lateral PFC	STN	ALIC
						Validation of the pathway identified in Li *et al.* (29)		

ALIC, anterior limb of the internal capsule; amSTN, anteromedial STN; BNST, bed nucleus of the stria terminalis; dACC, dorsal anterior cingulate cortex; DBS, deep brain stimulation; dlPFC, dorsolateral PFC; FTR, frontothalamic radiation; GPi, globus pallidus internus; GTS, Gilles de la Tourette syndrome; MD, medial dorsal; MFG, middle frontal gyrus; NAc, nucleus accumbens; OCD, obsessive-compulsive disorder; PFC, prefrontal cortex; STN, subthalamic nucleus; VC/VS, ventral capsule/ventral striatum; vlPFC, ventrolateral PFC; VTApp, ventral tegmental area projection pathway.

dimensions will further contribute to specific therapeutic outcomes (9). This is reflected by the fact that although a common pathway could be derived from connectomic studies in OCD DBS, there are evidently subjects in whom this pathway was not modulated but who still profited from DBS (29,32,34), implying that additional circuits will be relevant to consider. As an example (Figure S1), DBS for OCD is capable of changing affective states (i.e., anxiety, mood) that are accompanied by altered activity in a network comprising the vmPFC, insula, and amygdala (10). This is in line with changes in depression scores linked to modulation of a more ventrally located loop within the ALIC (which crucially does not involve the STN) (28). Congruent to this, it was recently shown that transcranial alternating-current stimulation of the OFC improved obsessive-compulsive behavior in a cohort of healthy subjects by interfering with reward-related beta-gamma oscillations (58). Given that antidepressant effects of DBS are likely to result from modulation of frontostriatal fibers (28), the frontostriatal input may also play a decisive role for improving affective states in OCD. The importance of this circuit for OCD DBS is also supported by animal studies showing that optogenetic stimulation of the OFC-VS pathway decreases grooming in a rodent model of OCD (55). A later study in the same OCD mouse model revealed that both DBS of the VS and ALIC resulted in a significant reduction in grooming independently (although the ALIC target was more effective on average), suggesting that both pathways are contributing to therapeutic success (59). Further evidence supporting the involvement of an affect-related circuitry stems from the comprehensively discussed study by Mosley *et al.*, where connectivity with the amygdala was also associated with DBS response, along with modulation of the central ALIC (1). These different therapeutic circuitries could correspond to improvement of different symptoms or neuropsychological dimensions of OCD. Thus, we emphasize that in the same manner as different basal ganglia cortical loops are implicated in the pathophysiology of OCD (9), neuromodulation of different circuits may contribute to therapeutic success.

Needless to say, other factors beyond targeting are likely to influence the outcome of OCD DBS as well, but so far, reliable response predictors are unknown. Larger volumes of the striatum seem to be associated with better outcomes (60), and a meta-analysis identified an association between age at OCD onset and presence of sexual/religious obsessions with beneficial outcomes (5), but effect sizes were small, and other clinical trials found no differences between outcomes across symptom dimensions (61). There is also uncertainty about optimal stimulation parameters for OCD, as systematic comparative studies hereof are lacking (62). Clinical trials of the ALIC/NAc/BNST region typically use high amplitudes [e.g., ranging from 3 to 7 V (61), 3.5 to 5 V (2), or targeted at 4.5 V (1)], while effective STN DBS required lower amplitudes [e.g., ranging from 1 to 4 V (63)]. In all of these trials, a monopolar high-frequency stimulation (>80 Hz) was applied, and the pulse width was mostly selected above 60 μsec, although often considerably higher (up to 120–450 μsec) for the ALIC/NAc/BNST area (61,64). For the previously discussed studies on connectomic DBS for OCD, no specific patient selection and similar stimulation parameters were chosen (1,30,32,33,61). Higher activation thresholds of fibers of passage (e.g., in the ALIC) over axons terminating in a nucleus (e.g., in the STN) may have led to differences in stimulation

amplitudes and pulse widths (65). Furthermore, on average and across centers, ALIC stimulation volume centers were more distant to the central ALIC target than in the STN groups—which could again explain lower stimulation amplitudes applied in the STN target.

LIMITATIONS AND METHODOLOGICAL CONSIDERATIONS

Connectomic DBS for OCD is a novel and emerging field that comes with relevant limitations. Primarily, the most studies relied on small cohorts (inherent to psychiatric DBS), which comes with a greater risk of false positive findings. Second, connectomic studies for DBS strongly depend on the validity of the modeled white matter pathways and how activation hereof is determined, which is again subject to relevant limitations. In case of OCD, many studies relied on a similar whole-brain normative connectome and fiber filtering approach based on isotropic electric field models (1,28,32–34). More complex biophysical field modeling methods have been developed that may lead to more detailed insights and superior results when predicting clinical effects, in the future (65–67). For a discussion on potential limitations of activation volume tractography (as performed in most OCD DBS studies, so far) versus tractography/pathway-activation models [as performed for instance in the study by Hartman *et al.* (25)], we refer to the excellent publication by Gunalan *et al.* (68). Third, until now, there is no prospective validation of the identified pathways in OCD DBS. Critically, prospective tractography-based DBS can result in substantial differences across centers, putatively because of differences in tractographic analysis (69). Despite these limitations, the field of connectomic DBS for OCD has made tremendous progress in the past years, and the current evidence stems from multiple centers using different targets and has been partly cross-validated using different connectivity estimates (e.g., dMRI and histology-based atlases). To face the obstacle of connectomic DBS for OCD, we call for future studies that 1) pool data from different centers for larger sample sizes, 2) focus on adequately assessed individual symptom/neuropsychological dimensions of OCD, 3) employ and ideally compare different approaches of DBS connectivity models, and 4) combine different neuromodulatory approaches for OCD. Finally, following the pioneering example of connectomic DBS for depression (70,71), prospective studies are now necessary to validate observations in DBS for OCD to make a step toward a more tailored, precise, and thus safe and effective neuromodulation for OCD.

CONCLUSIONS

In summary, we review evidence for a unified network spanning between cortical (the dACC, vlPFC, and assumingly others) and subcortical (anteromedial STN, medial dorsal nucleus of the thalamus) regions that—when modulated by means of DBS, ablative surgery, or noninvasive neuromodulation—alleviates obsessive-compulsive symptoms. We conclude that despite different uses of nomenclature, there is a high concordance between studies—especially regarding a specific surgical target site within the ALIC. Finally, we provide a mechanistic model with the most salient addition to include a limbic/associative hyperdirect pathway that traverses within the central segment of the ALIC as a critical component for clinical efficacy.

ACKNOWLEDGMENTS AND DISCLOSURES

This study is supported by the National Institutes of Health (Grant No. MH106435 [to SNH]); German Research Foundation (Deutsche Forschungsgemeinschaft, Project-ID 431549029 –SFB 1451 [to JCB] and Emmy Noether grants 410169619 and 424778381 – TRR 295 [to AH]); as well as Deutsches Zentrum für Luft- und Raumfahrt (DynaSti grant within the EU Joint Programme Neurodegenerative Disease Research [to AH]).

PEM has previously received an honorarium for lecturing from Boston Scientific and received an unrestricted educational grant from Medtronic. He is currently an investigator in clinical trials of deep brain stimulation for obsessive-compulsive disorder and anorexia nervosa. SAS reports consulting agreements with Boston Scientific, Abbott, Neuropace, Zimmier Biomet, and Koh Young. MB reports personal fees from Medtronic, Boston Scientific, Abbott (formerly St Jude), GE Medical, UCB, Bial, and IQWIG, and grants from Gondola, Felgenhauer-Stiftung, and Forschungspool Klinische Studien, outside the submitted work. All other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Neurology (JCB, MB), Department of Psychiatry and Psychotherapy (JCB, TS, SK, DH, JK), and Department of Stereotactic and Functional Neurosurgery (VV-V), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne; Department of Neurology, Movement Disorders and Neuromodulation Section (NL, BH, AH) and Einstein Center for Neurosciences (BH), Charité - University Medicine Berlin; Faculty of Philosophy (BH), Humboldt University of Berlin, Berlin School of Mind and Brain, Berlin; Department of Psychiatry (JK), Psychotherapy and Psychosomatic, Johanniter Hospital Oberhausen, Oberhausen, Germany; Department of Psychiatry (VV), Cambridge University, Cambridge, United Kingdom; Department of Psychiatry (MF), Mount Sinai Hospital, New York; Department of Pharmacology and Physiology (SNH), University of Rochester School of Medicine, Rochester, New York; Basic Neuroscience Division (SNH), Harvard Medical School, McLean Hospital, Belmont, Massachusetts; Department of Neurosurgery (SAS), Baylor College of Medicine, Houston, Texas; Department of Neurology (KAJ), Norman Fixel Institute for Neurological Diseases, University of Florida, Gainesville, Florida; Scientific Computing and Imaging Institute (CB) and Department of Biomedical Engineering (CB), University of Utah, Salt Lake City, Utah; Systems Neuroscience Group (PEM), QIMR Berghofer Medical Research Institute, Herston; Queensland Brain Institute (PEM), University of Queensland, St Lucia, Queensland, Australia; and School of Mental Health and Neuroscience (LA, TBvdV, AFGL), Maastricht University, Maastricht, the Netherlands.

Address correspondence to Juan Carlos Baldermann, M.D., at juan.baldermann@uk-koeln.de.

Received Feb 23, 2021; revised Jun 29, 2021; accepted Jul 1, 2021.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2021.07.010.

REFERENCES

1. Mosley PE, Windels F, Morris J, Coyne T, Marsh R, Giorni A, *et al.* (2021): A randomised, double-blind, sham-controlled trial of deep brain stimulation of the bed nucleus of the stria terminalis for treatment-resistant obsessive-compulsive disorder. Transl Psychiatry 11:190.
2. Denys D, Mantione M, Figee M, Van Den Munckhof P, Koerselman F, Westenberg H, *et al.* (2010): Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. Arch Gen Psychiatry 67:1061–1068.
3. Mallet L, Polosan M, Jaafari N, Baup N, Welter ML, Fontaine D, *et al.* (2008): Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med 359:2121–2134.

4. Wu H, Hariz M, Visser-Vandewalle V, Zrinzo L, Coenen VA, Sheth SA, *et al.* (2021): Deep brain stimulation for refractory obsessive-compulsive disorder (OCD): Emerging or established therapy? Mol Psychiatry 26:60–65.
5. Alonso P, Cuadras D, Gabriëls L, Denys D, Goodman W, Greenberg BD, *et al.* (2015): Deep brain stimulation for obsessive-compulsive disorder: A meta-analysis of treatment outcome and predictors of response. PLoS One 10:e0133591.
6. Kohl S, Schönherr DM, Luigjes J, Denys D, Mueller UJ, Lenartz D, *et al.* (2014): Deep brain stimulation for treatment-refractory obsessive compulsive disorder: A systematic review. BMC Psychiatry 14:214.
7. Figee M, Luigjes J, Smolders R, Valencia-Alfonso CE, Van Wingen G, De Kwaasteniet B, *et al.* (2013): Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder. Nat Neurosci 16:386–387.
8. Smith EE, Schüller T, Huys D, Baldermann JC, Ullsperger M, Allen JJ, *et al.* (2020): Prefrontal delta oscillations during deep brain stimulation predict treatment success in patients with obsessive-compulsive disorder. Brain Stimul 13:259–261.
9. Shephard E, Stern ER, van den Heuvel OA, Costa DLC, Batistuzzo MC, Godoy PBG, *et al.* (2021): Toward a neurocircuit-based taxonomy to guide treatment of obsessive-compulsive disorder [published online ahead of print Jan 7]. Mol Psychiatry.
10. Fridgeirsson EA, Figee M, Luigjes J, van den Munckhof P, Schuurman PR, van Wingen G, Denys D (2020): Deep brain stimulation modulates directional limbic connectivity in obsessive-compulsive disorder. Brain 143:1603–1612.
11. Barcia JA, Avecillas-Chasín JM, Nombela C, Arza R, García-Albea J, Pineda-Pardo JA, *et al.* (2019): Personalized striatal targets for deep brain stimulation in obsessive-compulsive disorder. Brain Stimul 12:724–734.
12. Li N, Hollunder B, Baldermann JC, Kibleur A, Treu S, Akram H, *et al.* (2021): A unified functional network target for deep brain stimulation in obsessive-compulsive disorder. Biol Psychiatry 90:701–713.
13. Banks GP, Nanda P, Patel R, Seth S (2019): Deep brain stimulation for obsessive compulsive disorder. In: Anderson WS, editor. Deep Brain Stimul. Stuttgart: Georg Thieme Verlag, 93–102.
14. Fodstad H, Strandman E, Karlsson B, West KA (1982): Treatment of chronic obsessive compulsive states with stereotactic anterior capsulotomy or cingulotomy. Acta Neurochir (Wien) 62:1–23.
15. Brown LT, Mikell CB, Youngerman BE, Zhang Y, McKhann GM 2nd, Sheth SA (2016): Dorsal anterior cingulotomy and anterior capsulotomy for severe, refractory obsessive-compulsive disorder: A systematic review of observational studies. J Neurosurg 124:77–89.
16. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B (1999): Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet 354:1526.
17. Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, *et al.* (2006): Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. Neuropsychopharmacology 31:2384–2393.
18. Sturm V, Lenartz D, Koulousakis A, Treuer H, Herholz K, Klein JC, Klosterkötter J (2003): The nucleus accumbens: A target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. J Chem Neuroanat 26:293–299.
19. Islam L, Franzini A, Messina G, Scarone S, Gambini O (2015): Deep brain stimulation of the nucleus accumbens and bed nucleus of stria terminalis for obsessive-compulsive disorder: A case series. World Neurosurg 83:657–663.
20. Coenen VA, Schlaepfer TE, Sajonz B, Döbrössy M, Kaller CP, Urbach H, Reisert M (2020): Tractographic description of major subcortical projection pathways passing the anterior limb of the internal capsule. Corticopetal organization of networks relevant for psychiatric disorders. Neuroimage Clin 25:102165.
21. Haber SN, Yendiki A, Jbabdi S (2021): Four deep brain stimulation targets for obsessive-compulsive disorder: Are they different? Biol Psychiatry 90:667–677.
22. Jiménez F, Nicolini H, Lozano AM, Piedimonte F, Salín R, Velasco F (2013): Electrical stimulation of the inferior thalamic peduncle in the treatment of major depression and obsessive compulsive disorders. World Neurosurg 80:S30.e17–S30.e25.
23. Coenen VA, Schlaepfer TE, Goll P, Reinacher PC, Voderholzer U, Tebartz Van Elst L, *et al.* (2017): The medial forebrain bundle as a target for deep brain stimulation for obsessive-compulsive disorder. CNS Spectr 22:282–289.
24. Horn A, Fox MD (2020): Opportunities of connectomic neuromodulation. Neuroimage 221:117180.
25. Hartmann CJ, Lujan JL, Chaturvedi A, Goodman WK, Okun MS, McIntyre CC, Haq IU (2016): Tractography activation patterns in dorsolateral prefrontal cortex suggest better clinical responses in OCD DBS. Front Neurosci 9:519.
26. Liebrand LC, Caan MWA, Schuurman PR, van den Munckhof P, Figee M, Denys D, van Wingen GA (2019): Individual white matter bundle trajectories are associated with deep brain stimulation response in obsessive-compulsive disorder. Brain Stimul 12:353–360.
27. Coenen VA, Panksepp J, Hurwitz TA, Urbach H, Mädler B (2012): Human medial forebrain bundle (MFB) and anterior thalamic radiation (ATR): Imaging of two major subcortical pathways and the dynamic balance of opposite affects in understanding depression. J Neuropsychiatry Clin Neurosci 24:223–236.
28. Baldermann JC, Melzer C, Zapf A, Kohl S, Timmermann L, Tittgemeyer M, *et al.* (2019): Connectivity profile predictive of effective deep brain stimulation in obsessive-compulsive disorder. Biol Psychiatry 85:735–743.
29. Li N, Baldermann JC, Kibleur A, Treu S, Akram H, Elias GJB, *et al.* (2020): A unified connectomic target for deep brain stimulation in obsessive-compulsive disorder. Nat Commun 11:3364.
30. Tyagi H, Apergis-Schoute AM, Akram H, Foltynie T, Limousin P, Drummond LM, *et al.* (2019): A randomized trial directly comparing ventral capsule and anteromedial subthalamic nucleus stimulation in obsessive-compulsive disorder: Clinical and imaging evidence for dissociable effects. Biol Psychiatry 85:726–734.
31. Petersen MV, Mlakar J, Haber SN, Parent M, Smith Y, Strick PL, *et al.* (2019): Holographic reconstruction of axonal pathways in the human brain. Neuron 104:1056–1064.e3.
32. Smith AH, Choi KS, Waters AC, Aloysi A, Mayberg HS, Kopell BH, Figee M (2021): Replicable effects of deep brain stimulation for obsessive-compulsive disorder. Brain Stimul 14:1–3.
33. van der Vlis TAMB, Ackermans L, Mulders AEP, Vrij CA, Schruers K, Temel Y, *et al.* (2021): Ventral capsule/ventral striatum stimulation in obsessive-compulsive disorder: Toward a unified connectomic target for deep brain stimulation? Neuromodulation 24:316–323.
34. Johnson KA, Duffley G, Foltynie T, Hariz M, Zrinzo L, Joyce EM, *et al.* (2021): Basal ganglia pathways associated with therapeutic pallidal deep brain stimulation for Tourette syndrome. Biol Psychiatry Cogn Neurosci Neuroimaging 6:961–972.
35. Dougherty DD, Chou T, Corse AK, Arulpragasam AR, Widge AS, Cusin C, *et al.* (2016): Acute deep brain stimulation changes in regional cerebral blood flow in obsessive-compulsive disorder. J Neurosurg 125:1087–1093.
36. Suetens K, Nuttin B, Gabriëls L, Van Laere K (2014): Differences in metabolic network modulation between capsulotomy and deep-brain stimulation for refractory obsessive-compulsive disorder. J Nucl Med 55:951–959.
37. Smith EE, Schüller T, Huys D, Baldermann JC, Andrade P, Allen JJ, *et al.* (2020): A brief demonstration of frontostriatal connectivity in OCD patients with intracranial electrodes. Neuroimage 220:117138.
38. Widge AS, Zorowitz S, Basu I, Paulk AC, Cash SS, Eskandar EN, *et al.* (2019): Deep brain stimulation of the internal capsule enhances human cognitive control and prefrontal cortex function. Nat Commun 10:1536.
39. Sheth SA, Mian MK, Patel SR, Asaad WF, Williams ZM, Dougherty DD, *et al.* (2012): Human dorsal anterior cingulate cortex neurons mediate ongoing behavioural adaptation. Nature 488:218–221.

40. McGovern RA, Sheth SA (2017): Role of the dorsal anterior cingulate cortex in obsessive-compulsive disorder: Converging evidence from cognitive neuroscience and psychiatric neurosurgery. J Neurosurg 126:132–147.
41. Sheth SA, Neal J, Tangherlini F, Mian MK, Gentil A, Cosgrove GR, *et al.* (2013): Limbic system surgery for treatment-refractory obsessive-compulsive disorder: A prospective long-term follow-up of 64 patients. J Neurosurg 118:491–497.
42. Shen L, Jiang C, Hubbard CS, Ren J, He C, Wang D, *et al.* (2020): Subthalamic nucleus deep brain stimulation modulates 2 distinct neurocircuits. Ann Neurol 88:1178–1193.
43. Coenen VA, Honey CR, Hurwitz T, Rahman AA, McMaster J, Bürgel U, Mädler B (2009): Medial forebrain bundle stimulation as a pathophysiological mechanism for hypomania in subthalamic nucleus deep brain stimulation for Parkinson's disease. Neurosurgery 64:1106–1114.. discussion 1114–1115.
44. Nieuwenhuys R, Voogd J, van Huijzen C (2008): The Human Central Nervous System: A Synopsis and Atlas, 4th ed. Heidelberg: Springer.
45. Ding SL, Royall JJ, Sunkin SM, Ng L, Facer BAC, Lesnar P, *et al.* (2016): Comprehensive cellular-resolution atlas of the adult human brain. J Comp Neurol 524:3127–3481.
46. Mai JK, Paxinos G (2012): The Human Nervous System, 3rd ed. San Diego: Academic Press.
47. Coenen VA, Schlaepfer TE, Varkuti B, Schuurman PR, Reinacher PC, Voges J, *et al.* (2019): Surgical decision making for deep brain stimulation should not be based on aggregated normative data mining. Brain Stimul 12:1345–1348.
48. Safadi Z, Grisot G, Jbabdi S, Behrens TE, Heilbronner SR, McLaughlin NCR, *et al.* (2018): Functional segmentation of the anterior limb of the internal capsule: Linking white matter abnormalities to specific connections. J Neurosci 38:2106–2117.
49. Dougherty DD, Baer L, Cosgrove GR, Cassem EH, Price BH, Nierenberg AA, *et al.* (2002): Prospective long-term follow-up of 44 patients who received cingulotomy for treatment-refractory obsessive-compulsive disorder. Am J Psychiatry 159:269–275.
50. Carmi L, Tendler A, Bystritsky A, Hollander E, Blumberger DM, Daskalakis J, *et al.* (2019): Efficacy and safety of deep transcranial magnetic stimulation for obsessive-compulsive disorder: A prospective multicenter randomized double-blind placebo-controlled trial. Am J Psychiatry 176:931–938.
51. Robbins TW, Vaghi MM, Banca P (2019): Obsessive-compulsive disorder: Puzzles and prospects. Neuron 102:27–47.
52. Milad MR, Rauch SL (2012): Obsessive-compulsive disorder: Beyond segregated cortico-striatal pathways. Trends Cogn Sci 16:43–51.
53. Insel TR (2014): The NIMH Research Domain Criteria (RDoC) project: Precision medicine for psychiatry. Am J Psychiatry 171:395–397.
54. Ahmari SE, Spellman T, Douglass NL, Kheirbek MA, Simpson HB, Deisseroth K, *et al.* (2013): Repeated cortico-striatal stimulation generates persistent OCD-like behavior. Science 340:1234–1239.
55. Burguière E, Monteiro P, Feng G, Graybiel AM (2013): Optogenetic stimulation of lateral orbitofronto-striatal pathway suppresses compulsive behaviors. Science 340:1243–1246.
56. Rodriguez-Romaguera J, Do-Monte FH, Tanimura Y, Quirk GJ, Haber SN (2015): Enhancement of fear extinction with deep brain stimulation: Evidence for medial orbitofrontal involvement. Neuropsychopharmacology 40:1726–1733.
57. van den Heuvel OA, van Wingen G, Soriano-Mas C, Alonso P, Chamberlain SR, Nakamae T, *et al.* (2016): Brain circuitry of compulsivity. Eur Neuropsychopharmacol 26:810–827.
58. Grover S, Nguyen JA, Viswanathan V, Reinhart RMG (2021): High-frequency neuromodulation improves obsessive-compulsive behavior. Nat Med 27:232–238.
59. Pinhal CM, van den Boom BJG, Santana-Kragelund F, Fellinger L, Bech P, Hamelink R, *et al.* (2018): Differential effects of deep brain stimulation of the internal capsule and the striatum on excessive grooming in Sapap3 mutant mice. Biol Psychiatry 84:917–925.
60. Liebrand LC, Zhutovsky P, Tolmeijer EK, Graat I, Vulink N, de Koning P, *et al.* (2021): Deep brain stimulation response in obsessive–compulsive disorder is associated with preoperative nucleus accumbens volume. Neuroimage Clin 30:102640.
61. Huys D, Kohl S, Baldermann JC, Timmermann L, Sturm V, Visser-Vandewalle V, Kuhn J (2019): Open-label trial of anterior limb of internal capsule-nucleus accumbens deep brain stimulation for obsessive-compulsive disorder: Insights gained. J Neurol Neurosurg Psychiatry 90:805–812.
62. van Westen M, Rietveld E, Figee M, Denys D (2015): Clinical outcome and mechanisms of deep brain stimulation for obsessive-compulsive disorder. Curr Behav Neurosci Rep 2:41–48.
63. Chabardes S, Krack P, Piallat B, Bougerol T, Seigneuret E, Yelnik J, *et al.* (2020): Deep brain stimulation of the subthalamic nucleus in obsessive-compulsives disorders: Long-term follow-up of an open, prospective, observational cohort. J Neurol Neurosurg Psychiatry 91:1349–1356.
64. Luyten L, Hendrickx S, Raymaekers S, Gabriëls L, Nuttin B (2016): Electrical stimulation in the bed nucleus of the stria terminalis alleviates severe obsessive-compulsive disorder. Mol Psychiatry 21:1272–1280.
65. Bower KL, Mcintyre CC (2020): Deep brain stimulation of terminating axons. Brain Stimul 13:1863–1870.
66. Noecker AM, Frankemolle-Gilbert AM, Howell B, Petersen MV, Beylergil SB, Shaikh AG, McIntyre CC (2021): StimVision v2: Examples and applications in subthalamic deep brain stimulation for Parkinson's disease. Neuromodulation 24:248–258.
67. Howell B, Isbaine F, Willie JT, Opri E, Gross RE, De Hemptinne C, *et al.* (2021): Image-based biophysical modeling predicts cortical potentials evoked with subthalamic deep brain stimulation. Brain Stimul 14:549–563.
68. Gunalan K, Chaturvedi A, Howell B, Duchin Y, Lempka SF, Patriat R, *et al.* (2017): Creating and parameterizing patient-specific deep brain stimulation pathway-activation models using the hyperdirect pathway as an example. PLoS One 12:e0176132.
69. Ramasubbu R, Clark DL, Golding S, Dobson KS, Mackie A, Haffenden A, Kiss ZH (2020): Long versus short pulse width subcallosal cingulate stimulation for treatment-resistant depression: A randomised, double-blind, crossover trial. Lancet Psychiatry 7:29–40.
70. Riva-Posse P, Choi KS, Holtzheimer PE, Crowell AL, Garlow SJ, Rajendra JK, *et al.* (2018): A connectomic approach for subcallosal cingulate deep brain stimulation surgery: Prospective targeting in treatment-resistant depression. Mol Psychiatry 23:843–849.
71. Crowell AL, Riva-Posse P, Holtzheimer PE, Garlow SJ, Kelley ME, Gross RE, *et al.* (2019): Long-term outcomes of subcallosal cingulate deep brain stimulation for treatment-resistant depression. Am J Psychiatry 176:949–956.
72. Rasmussen SA, Norén G, Greenberg BD, Marsland R, McLaughlin NC, Malloy PJ, *et al.* (2018): Gamma ventral capsulotomy in intractable obsessive-compulsive disorder. Biol Psychiatry 84:355–364.
73. Jung HH, Chang WS, Kim SJ, Kim CH, Chang JW (2018): The potential usefulness of magnetic resonance guided focused ultrasound for obsessive compulsive disorders. J Korean Neurosurg Soc 61:427–433.
74. D'Astous M, Cottin S, Roy M, Picard C, Cantin L (2013): Bilateral stereotactic anterior capsulotomy for obsessive-compulsive disorder: Long-term follow-up. J Neurol Neurosurg Psychiatry 84:1208–1213.
75. Onesti E, Gabriele M, Cambieri C, Ceccanti M, Raccah R, Di Stefano G, *et al.* (2013): H-coil repetitive transcranial magnetic stimulation for pain relief in patients with diabetic neuropathy. Eur J Pain 17:1347–1356.
76. Mai JK, Paxinos G, Voss T (2007): Atlas of the Human Brain, 3rd ed. San Diego: Academic Press.