ARTICLE

Tractography-based versus anatomical landmark-based targeting in vALIC deep brain stimulation for refractory obsessive-compulsive disorder

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Deep brain stimulation (DBS) of the ventral anterior limb of the internal capsule (vALIC) is effective for refractory obsessive-compulsive disorder (OCD). Retrospective evaluation showed that stimulation closer to the supero-lateral branch of the medial forebrain bundle (slMFB), within the vALIC, was associated with better response to DBS. The present study is the first to compare outcomes of DBS targeted at the vALIC using anatomical landmarks and DBS with connectomic tractography-based targeting of the slMFB. We included 20 OCD-patients with anatomical landmark-based DBS of the vALIC that were propensity score matched to 20 patients with tractography-based targeting of electrodes in the slMFB. After one year, we compared severity of OCD, anxiety and depression symptoms, response rates, time to response, number of parameter adjustments, average current, medication usage and stimulation-related adverse effects. There was no difference in Y-BOCS decrease between patients with anatomical landmark-based and tractography-based DBS. Nine (45%) patients with anatomical landmark-based DBS and 13 (65%) patients with tractography-based DBS were responders ($BF_{10} = 1.24$). The course of depression and anxiety symptoms, time to response, number of stimulation adjustments or medication usage did not differ between groups. Patients with tractography-based DBS experienced fewer stimulation-related adverse effects than patients with anatomical landmark-based DBS (38 vs 58 transient and 1 vs. 17 lasting adverse effects; $BF_{10} = 14.968$). OCD symptoms in patients with anatomical landmark-based DBS of the vALIC and tractography-based DBS of the slMFB decrease equally, but patients with tractography-based DBS experience less adverse effects.

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INTRODUCTION

Deep brain stimulation (DBS) is a multidisciplinary treatment for severe refractory obsessive-compulsive disorder (OCD). DBS modulates abnormal neuronal activity through electrodes, which for OCD are usually targeted around the Cortico-Striato-Thalamo-Cortical (CSTC)-network. Targets include the subthalamic nucleus (STN), the ventral striatum (VS), the anterior limb of the internal capsule (ALIC) and, more recently, the supero-lateral branch of the medial forebrain bundle (slMFB) [1–5]. Different targeting strategies have comparable overall effectiveness in reducing OCD symptoms [1]. Ongoing efforts to optimize DBS targeting in OCD have the aim to further increase effectiveness and decrease side effects.

Thus far, evaluation of DBS targeting was limited by i.a. imaging techniques. However, novel tractography techniques based on diffusion magnetic resonance imaging (MRI) have shown to successfully visualize fiber tracts like the slMFB [6]. In addition, expanding knowledge about the human connectome has helped to identify neural networks involved in OCD. This has resulted in a novel targeting strategy that focusses on neural networks, rather than separate nuclei; connectomic DBS [4]. Connectomic DBS may further personalize DBS therapy for OCD and reduce the variability of individual outcomes.

Recently, our group presented observational evidence showing that within the vALIC, active stimulation closer to the slMFB was associated with better treatment outcomes in OCD than stimulation closer to the anterior thalamic radiation [7]. This suggested that patients with OCD could benefit more from DBS specifically targeted at the slMFB. In addition, a retrospective study using normative connectomic data of 50 patients with DBS for OCD targeted at different structures (ALIC, STN and nucleus accumbens), suggested that a common fiber bundle, the slMFB, was associated with clinical response [8].

On the basis of the aforementioned results, we started targeting the slMFB within the vALIC using diffusion weighted imaging (DWI)-MRI to visualize individual fiber tracts. To the best of our knowledge, this is the first study to compare deterministic tractography-based DBS with the slMFB as target, to anatomical landmark-based DBS aimed at the vALIC. We compare outcomes of 20 refractory OCD patients who received DBS of the vALIC using

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targeting based on anatomical landmarks ("conventional DBS") and 20 refractory OCD-patients with DBS targeted at the slMFB within the vALIC using tractography ("tractography-based DBS"). We used individual DWI data rather than normative data, enabling a personalized DBS treatment. We compared the decrease of OCD symptoms during the first year of DBS. Secondary, we compared anxiety and depressive symptoms, response rates, time to response, number of stimulation-setting-adjustments, adverse effects, average current needed and medication usage.

MATERIAL AND METHOD

Patients and study design

Data for this study was collected from electronic records of outpatients that received DBS for refractory OCD at the Amsterdam University Medical Centers between June 2010 and September 2020. For patients that underwent DBS surgery between June 2010 and October 2017, targeting was based on anatomical landmarks on a structural MRI scan. From November 2017 onwards, targeting was based on deterministic tractography using DWI-MRI scans. All consecutive patients who received tractography-based DBS with a follow-up of at least one year were included. From the cohort of patients with conventional DBS, we selected a matched group using propensity scores (more detailed description below). The medical ethical committee of the Academic Medical Center concluded that this study did not need formal ethical approval. Written informed consent for the use of data was obtained from all included patients.

Inclusion criteria for DBS were a ≥5 year history of primary OCD with a baseline Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of ≥28 and no or insufficient response to the following treatments: two selective serotonin reuptake inhibitors (SSRI) at maximum dosage for 12 weeks at maximum dosage, clomipramine for 12 weeks at maximum dosage, one augmentation trial with an atypical anti-psychotic and SSRI for 8 weeks and ≥16 sessions of cognitive-behavioral therapy (CBT). Exclusion criteria for DBS were psychotic disorders, substance abuse within the past 3 months, and unstable neurological or coagulation disorders.

Image acquisition

Prior to DBS surgery, MRI scanning was performed on a 3T Elition Ingenia (Philips, Best, The Netherlands) equipped with a 32-channel receive coil (Philips). The 3D saggital T1-weighted gadolinium-enhanced images were acquired with the following parameters: repetition time 8.81 ms; echo time 4.03 ms; echo train length 242; field of view 256 mm; slice thickness 0.9 mm; scan time 8 min. 3D axial T2-weighted scans had the following parameters: repetition time 2500 ms; echo time 230 ms; echo train length 133; field of view 250 mm; slice thickness 1.1 mm; scan time 3 min. For DWI scanning we used the following parameters: repetition time 8234 ms; echo time 96 ms; $b = 1200$ s/mm^2, 32 gradient directions; phase encoding anterior-posterior, no reverse encoding; field of view 256 mm; slice thickness 2.0 mm; scan time 14 min.

Tractography-based surgical planning

For tractography-based DBS, surgical planning was completed with Brainlab Elements software (Brainlab AG, Munich, Germany), allowing for deterministic tractography based on the DWI model. First, the DWI series was coregistered to the structural images, followed by automatic image distortion correction, after which the results were scrutinized thoroughly. We created a region of interest (ROI) on T2 images in the vALIC and used the vALIC ROI in conjunction with a midbrain ROI encompassing the ventral tegmental area (VTA) to extract the slMFB, using default Brainlab settings for fractional anisotropy (FA, 0.2), minimum length (80 mm) and maximum angulation (20°).

Targeting and DBS surgery

Before surgery, a stereotactic frame was attached to the patient's head under general anesthesia and the patient underwent a frame-based 1.5 T MRI scan or (since 2018) a frame-based cone beam computed tomography (O-arm O2 imaging system; Medtronic, Minneapolis, USA). The 3T scan and stereotactic 1.5 T/cone beam CT scan were co-registered with BrainLab to enable planning in stereotactic space. Electrodes (model 3389 with 1.5 mm contacts and 0.5 mm interspace, Medtronic, Minneapolis, MN, USA) were implanted bilaterally.

In conventional landmark-based DBS planning, the starting point for target determination relative to the intercommissural line was 7 mm lateral of the midline, 3 mm anterior to the anterior border of the anterior commissure and 4 mm inferior to the intercommissural line. The target localization was then adjusted based on individual anatomical representation of the nucleus accumbens (NAc) and ALIC. The angle in the sagittal plane was slightly anterior (±75° to the intercommissural line) and the angle in the coronal plane was determined by the contours of the ALIC. The deepest contact of the quadripolar electrode was implanted in the NAc and the upper three contacts in the vALIC.

For tractography-based DBS, planning was started in the same manner on structural images, but the trajectory was then adjusted using the projection of the tractography-based slMFB that was acquired using DWI (Fig. 1). The deepest contact of the electrode was implanted just ventral of the course of the slMFB within the vALIC, with the upper three contacts positioned in the slMFB. For most patients this led to a more dorsal position of the electrode and the bottom contact did not end up in the Nac.

DBS treatment protocol

Detailed information about the DBS protocol was published previously [2]. Summarizing, DBS was activated two weeks after surgery. Effectiveness and adverse effects were evaluated by clinicians every 2 weeks in order to optimize DBS parameter settings to achieve a stable reduction of obsessions and compulsions, while minimizing adverse effects. The two middle contact points were activated at a voltage of 3 V, frequency of 130 Hz and pulse width of 90 µs. Parameter settings were adjusted according to protocol, first increasing the voltage, then pulse width and at last changing contact points. Additionally, patients were offered cognitive behavioral treatment (CBT) when a patient was motivated and Y-BOCS score had decreased sufficiently in order to give resistance to compulsions [9]. In case of remission of OCD, no CBT was added.

Outcome measures

The primary outcome measure was the course of Y-BOCS scores during the first year of DBS. The Y-BOCS is a clinician-rated scale with scores ranging from 0 to 40 designed to assess symptoms of OCD [10]. Secondary, we looked at the number of responders in both groups after one year of DBS. Patients were considered to be responders if the Y-BOCS score decreased with at least 35% and partial responders if the score decreased between 25% and 34%. Patients were considered non-responders if they had a score decrease less than 25%. Additionally, symptoms of anxiety were assessed with the Hamilton Anxiety Rating Scale (HAM-A [11]), and symptoms of depression with the 17-item Hamilton Depression Rating Scale (HAM-D [12]). Other secondary outcome measures were number of days till response, number of parameter adjustments and voltage-applied current and medication usage at 1-year follow-up. Data on stimulation-related adverse events were acquired from spontaneous reports by the patient, by questioning, or by observation. Adverse events were categorized as transient when they vanished spontaneously or after adjustments in stimulation settings and as permanent if they were still present at the end of the study. Adverse events were classed as

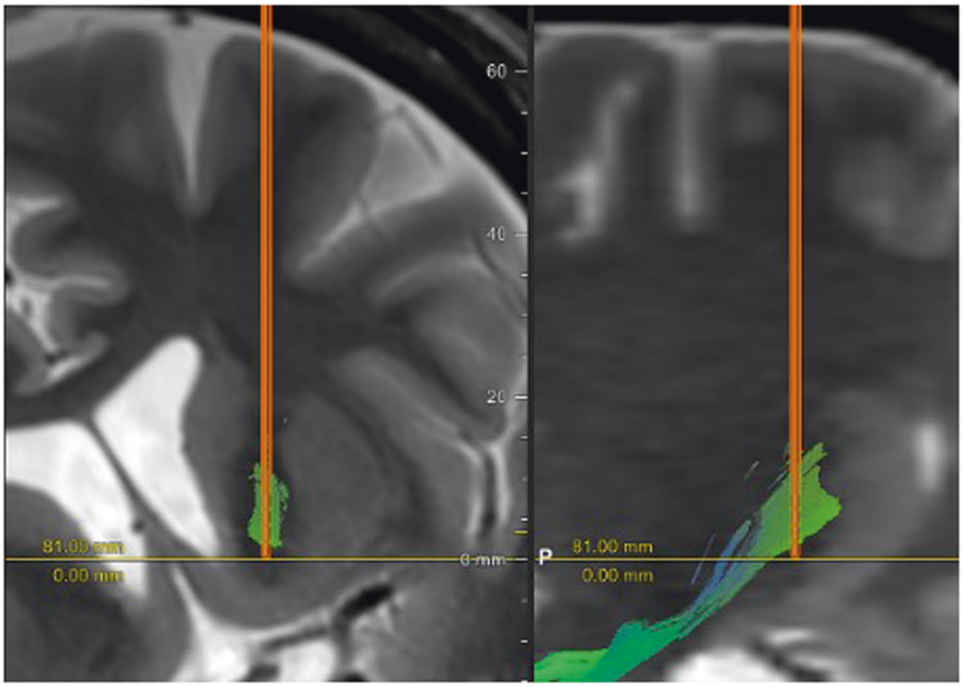

Fig. 1 Tractographic planning. Inline coronal (left panel) and sagittal (righ panel) tractographic planning of deep brain stimulation quadripolar electrode in the supero lateral branch of medial forebrain bundle during its course through the anterior limb of the internal capsule in a patient with refractory obsessive-compulsive disorder.

serious adverse events (SAE) when it was life-threatening, resulted in significant disability or death, or required hospitalization.

Propensity score matching

Each patient with tractography-based DBS was matched to a patient from the pool of patients with anatomical landmark-based DBS using propensity scores [13]. We used package 'MatchIt' in R (version 3.6.1) for propensity score matching [14]. The following demographic variables were used to build the propensity score: sex, age, age of OCD onset, baseline Y-BOCS score, baseline HAM-D score, and presence of a personality disorder. These variables were chosen based on previous predictor studies and availability [15, 16]. Two baseline HAM-D scores were missing and were imputed using multiple imputation to improve matching.

Statistical analyses

Differences in Y-BOCS scores over time between the two groups during the first year of DBS were analyzed using linear mixed models, with Y-BOCS scores as the criterion and fixed effects of group, time since DBS surgery (in days) and stimulation (on vs. off) on subject-specific slopes and with default mode for prior odds. Time in days was log-transformed to ensure a linear relationship between predictor and dependent variable. Similar models were estimated for HAM-A and HAM-D scores. We primarily performed Bayesian mixed models, and added classical frequentist mixed models as a sensitivity analysis (2-tailed α of .05). Response rates were analyzed with Bayesian Chi-square tests. Differences in time to response, number of parameter adjustments, and voltage at 12-month follow-up were analyzed using Bayesian t-tests. Adverse events in both groups were analyzed using a Bayesian Mann Whitney U test. At last, medication use in both groups were analyzed results with a Bayesian chi-square test. Because the present study is the first to compare conventional DBS to tractography-based DBS in OCD, we did not use directional priors. Our H0 hypothesis was that there is no difference between tractography-based vs conventional landmark-based DBS and our H1 or alternative hypothesis was that there is a difference between tractography-based vs conventional landmark-based DBS. Analyses were executed in JASP (version 0.15, Amsterdam, The Netherlands). We considered Bayes factors 0.33–3 to be weak (meaning no to little difference the in plausibility of either H0 or H1 to predict the data), 0.1–0.33 or 3–10 moderate evidence for H0 or H1 respectively, and <0.1 or >10 strong evidence for H0 or H1, respectively [17].

RESULTS

Demographics and propensity score matching

Using propensity score matching, 20 consecutive patients with tractography-based DBS were matched to 20 patients with conventional DBS who were selected from a pool of 43 conventional DBS patients. Baseline variables of the two groups did not differ, indicating that matching was successful (Table 1).

Effectiveness of tractography-based vs conventional landmark-based DBS

During the first year of DBS, the average Y-BOCS score in the conventional DBS group decreased with 12 points (37%) from 32 (SD 5) to 20 (SD 11) points (Fig. 2). In the tractography-based DBS group the average Y-BOCS score decreased with 14 points (42%) from 32 (SD 5) to 19 (SD 10). Primary Bayesian analysis showed no difference in course of the Y-BOCS between groups ($B = -0.096$; SD = 1.1, see supplement Table 1). Also according to the sensitivity frequentist analyses there was no significant difference between groups ($F(134.81) = 0.010$, $p = 0.921$). Nine (45%) out 20 patients with conventional DBS were responder, 3 partial responder (15%) and 8 non-responder (40%). Thirteen (65%) out of 20 patients with tractography-based DBS were responder, 1 partial responder (5%) and 6 non-responder (30%). Despite the numerical difference in response rates between the tractography-based and conventional DBS groups, there was only weak evidence for the alternative hypothesis ($BF_{10} = 1.24$).

As a secondary analysis, we compared the course of the HAM-D and HAM-A scores during the first year of DBS in the two groups

Table 1. Demographics of obsessive-compulsive disorder patients with conventional deep brain stimulation (DBS) ($N = 20$) and tractography-based DBS ($N = 20$).

	Conventional DBS ($N = 20$)	Tractography-based DBS ($N = 20$)	BF_{10}
Sex (male/female)	4/16	5/15	2.144
Age at surgery (M/SD)	39.25 (11.9)	41.1 (14.3)	2.635
Age of OCD onset (M/SD)	19.5 (10.1)	21.4 (12.6)	2.917
Presence of a personality disorder (n/N)	4 (20)	2 (20)	1.433
Baseline Y-BOCS score (M/SD)	31.5 (4.8)	32.2 (4.7)	2.967
Baseline HAM-D score (M/SD)	18.9 (5.2)	16.3 (6.4)	1.557
Baseline HAM-A score (M/SD)	24.1 (7.9)	28.7 (10.4)	1.289
Baseline BABS score (M/SD)	9.6 (6.6)	8.3 (6.7)	2.313

Y-BOCS Yale-Brown Obsessive Compulsive Scale. *HAM-D* Hamilton Depression Rating Scale. *HAM-A* Hamilton Anxiety Scale. *BABS* Brown Assessment of Believe Scale

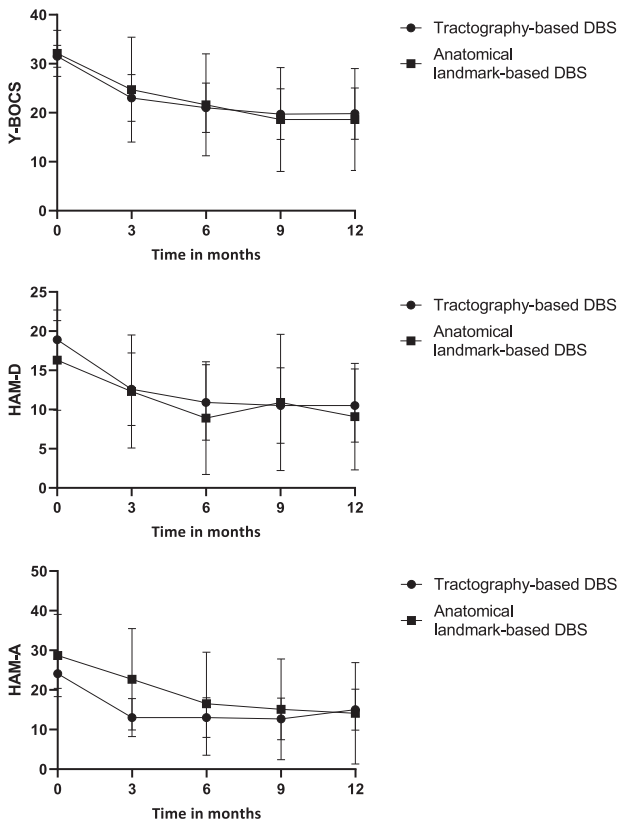

Fig. 2 Clinical symptom scores. Average scores on the Y-BOCS (Yale-Brown Obsessive Compulsive Scale), HAM-D (Hamilton Depression Rating Scale), and HAM-A (Hamilton Anxiety Scale) in patients with tractography-based deep brain stimulation (DBS) ($N = 20$) and anatomical landmark-based DBS ($N = 20$).

(Fig. 1). In the conventional DBS-group the average HAM-D score decreased with 8.4 points (44%) from 18.9 (SD 5) to 11 (SD 10). In the tractography-based DBS group the average HAM-D score decreased with 7 points (44%), from 16 (SD 6) to 9 (SD 6). The groups did not differ on course of the HAM-D ($B = -0.924$; SD = 0.751, see supplement Table 2). There was no significant difference between groups ($F(129.73) = 1.766$, $p = 0.194$). In the conventional DBS-group the average HAM-A score decreased with 9 points (38%) from 24 (SD 8) to 15 (SD 11). In the tractography-based DBS group the average HAM-A score decreased with 15 points (51%) from 29 (SD 10) to 14 (SD 13). The groups did not differ on course of the HAM-A ($B = -1.977$; SD = 1.168, see supplement Table 3) and there was no significant difference ($F(122.12) = 2.803$, $p = 0.108$).

There was weak evidence for the alternative hypothesis that there was a difference between groups in average time to response, number of parameter adjustments, and medication usage at 1-year follow-up (Table 2). After 1 year of DBS, patients with conventional DBS had an average voltage-controlled current of 5.9 Ampere (SD 1.1) and patients with tractography-based DBS of 7.2 Ampere (SD 1.6). There was moderate evidence for the alternative hypothesis that patients with conventional and tractography-based DBS receive different currents ($BF_{10} = 7.601$).

Adverse events

Overall, there was strong evidence that patients with tractography-based DBS experience less stimulation-related adverse events than patients with conventional DBS ($BF_{10} = 14.968$). Patients with conventional DBS reported in total 58 transient adverse events and 17 lasting adverse events whereas patients with tractography-based DBS reported 38 transient adverse events and 1 lasting adverse event (Table 3). In the group of patients with conventional DBS, 11 patients experienced symptoms of hypomania compared to 3 in the group with tractography-based DBS. In the group with tractography-based DBS two serious adverse events (SAE) occurred; one patient attempted suicide and one patient experienced a manic episode when the DBS was turned on, which required psychiatric ward admission. The suicide attempt occurred when the DBS was turned off, so was not related to stimulation. In the group with conventional DBS, 1 SAE (mania requiring psychiatric admission) was reported.

DISCUSSION

To the best of our knowledge, this is the first study to directly compare tractography-based DBS with slMFB as target to anatomical-landmark based DBS of the vALIC for refractory OCD. We showed that tractography-based DBS does not result in a stronger decrease of OCD symptoms than conventional DBS. However, patients with tractography-based DBS experience 60% less stimulation-related adverse effects than patients with conventional DBS.

Several observational studies on slMFB as a DBS target for OCD were promising [7, 8]. Yet, we found that DBS prospectively targeted at the slMFB using DWI is not superior to conventional vALIC DBS in reducing OCD symptoms. A potential explanation for the lack of higher efficacy with tractography-based DBS is that effect sizes of conventional vALIC-DBS for OCD already are among the largest in psychiatry [1] and a ceiling effect may prevented from establishing a superior effect of DWI targeting in terms of

Table 2. Outcomes of conventional deep brain stimulation (DBS) ($N = 20$) and tractography-based DBS ($N = 20$) in patients with obsessive-compulsive disorder.

	Conventional DBS ($N = 20$)	Tractography-based DBS ($N = 20$)	BF_{10}
Y-BOCS at 1-year follow-up (M/SD)	19.8 (11.2)	18.6 (10.4)	.
HAM-D at 1-year follow-up (M/SD)	10.5 (10.0)	9.1 (6.8)	.
HAM-A at 1-year follow-up (M/SD)	15.0 (11.1)	14.1 (12.8)	.
Responders (*n*)	9	13	1.24
Average time to response in days (M/SD)	107.3 (91.4)	98.1 (68.7)	2.701
Number of parameter adjustments during first year of DBS (M/SD)	10.5 (7.7)	7.9 (5.2)	2.701
Average current at 1-year follow-up in Ampere (M/SD)	5.9 (1.1)	7.2 (1.6)	7.601
Patients with less prescribed medication at 1-year follow-up (*n*)	8	5	1.746

Y-BOCS Yale-Brown Obsessive Compulsive Scale. *HAM-D* Hamilton Depression Rating Scale. *HAM-A* Hamilton Anxiety Scale.

average symptom reduction. In contrast to previous observational studies, a recent study by Widge et al. found that stimulation of different white-matter tracts in the ventral striatum/ventral capsule could not predict individual response to DBS in eight patients [18]. These authors stressed that group-level significant correlations often do not have clinical predictive power. In addition, the reliability of tractography is still ambiguous. Tractography can be deceptive since it estimates the possible course of the white matter bundle and can vary highly depending on the ROIs used. A previous ground truth study showed that tractograms contain 90% of the targeted bundle, but also many other, invalid bundles [5]. Therefore, tractography-based DBS might not (yet) better than anatomical landmark-based DBS, which may change when tractographic techniques improve. At last, we want to emphasize that it is unlikely that our anatomical landmark-based targeting was as accurate in targeting the slMFB as our tractography-based targeting, since Liebrand et al. previously found that the slMFB was outside the volume of activated tissue in 37.5% of landmark-based tracts [7].

Though the average decrease in symptoms did not differ between groups, the response rate was 20% higher in patients with tractography-based DBS compared to conventional DBS. A 20% increase in response rate is clinically important, but the statistical evidence was weak, possibly due to a lack of power. We cannot yet draw the conclusion that tractography-based DBS increases the likelihood to response to DBS in OCD but our results emphasize the need for larger studies comparing tractography-based and conventional DBS.

Patients with tractography-based DBS reported less adverse effects than patients with conventional DBS. The most common adverse effects of conventional and tractography-based DBS were hypomanic symptoms, sleeping problems, and impulsivity, which is in line with previous research [19]. Both conventional and tractography-based DBS resulted in one patient with transient manic symptoms. We observed *less* hypomanic symptoms in patients with tractography-based DBS of the slMFB. The slMFB is known to have a strong effect on affective symptoms [20]. However, transient hypomanic symptoms occur as an adverse effect of DBS targeted at different brain structures, including the vALIC and STN [21]. A previous case-study including two OCD patients with tractography-based DBS of the slMFB [3] reported no adverse effects. In this study, the electrodes were targeted in the same bundle, but closer to the STN in the VTA. The mechanism by which tractography-based DBS may reduce adverse effects remains unknown. Possiblymore precise stimulation of networks involved in OCD may minimize adverse effects by surpassing the surrounding neural elements. For most patients with tractography-based DBS of the slMFB, the bottom contact of the electrodes did not end up in the Nac. Stimulation of the NAc has been associated with stimulation-induced hypomanic symptoms [22]. By surpassing the NAc, patients with tractography-based DBS potentially experienced less hypomanic symptoms.

At present, there is an ongoing discussion about the nomenclature used to describe the white matter target that we refer to as slMFB [23]. Some say that the slMFB should be named otherwise since the classic MFB contains tyrosine hydroxylase–positive fibers, while the ALIC does not [24, 25]. Criticists of the slMFB state that the fibers running through the ALIC are hyperdirect corticothalamic fibers, running to the thalamus, STN and brainstem regions [26, 27]. However, a recent study combining tractographic and histological data showed that both hyperdirect corticothalamic fibers *and* the cortico-tegmental projections of the slMFB are present in the internal capsule [28]. The authors found that DBS did not modulate the corticothalamic fibers but only the cortico-tegmental projections. In line with this recent work, we chose to use the name slMFB for the bundle running through the ALIC, connecting the VTA and the prefrontal cortical areas.

Our study has several strengths and limitations. This is the first study to directly compare two different targeting methods and a sample size of 40 patients is considered large in the field of DBS for OCD. However, since effects sizes of conventional DBS are already high, this study is likely not to have enough power to find a small difference between conventional and tractography-based DBS. In addition, this was a non-randomized study, meaning that other factors besides targeting may have influenced our results. All patients with conventional DBS underwent surgery between June 2010 and October 2017 and patients with tractography-based DBS between November 2017 and September 2020. Therefore, various changes over time may have influenced the results. However, we tried to control for as many confounding factors as possible, by matching patients with tractography-based DBS to patients with anatomic landmark-based DBS using propensity scores. At last, a strength of the present study is that we did not use normative connectomic data but patient-specific DWI-images, which are more reliable [29].

Though tractography-based DBS was not followed by more symptom decrease than conventional DBS, the finding that patients with tractography-based DBS experience less adverse effects than patients with conventional DBS is clinically important. Tractographical targeting has no extra risks though it requires targeting software that can incorporate DWI. Future studies may provide more insight into the reliability, accuracy, and efficacy of tractography-based DBS in OCD with slMFB as target. In addition, larger studies with more power are needed to confirm our statistically weak finding that patients with tractography-based DBS more often respond than patients with conventional DBS.

Stimulation of the slMFB has been associated with improvements of mood [8]. The slMFB is part of an affective network that also involves the medial orbitofrontal cortex (OFC) [30–32].

Table 3. Stimulation related adverse events and serious adverse events (SAE) in patients with conventional deep brain stimulation (DBS) ($N = 20$) and tractography-based DBS ($N = 20$).

Adverse event	Conventional DBS ($N = 20$) Transient/ permanent	Tractography-based DBS ($N = 20$) Transient/ permanent
Suicide attempt (SAE)	0/0	1/0
Mania (SAE)	1/0	1/0
Suicidal thoughts	3/0	2/0
Hypomanic symptoms following stimulation adjustments (euphoria, hyperactivity, insomnia, restlessness, impulsivity)	11/0	3/0
Manic episode following stimulation adjustments	0/0	1/0
Irritability	4/1	4/0
Sleeping problems	10/2	5/0
Fatigue	4/2	2/0
Restlessness	6/2	8/0
Panic attacks	2/0	0/0
Impulsivity	5/0	1/0
Increased libido	2/0	0/0
Sensitivity to sound	0/1	0/0
Psychotic symptoms (hallucinations and delusions)	1/0	1/0
Tics	2/0	0/1
Depressive symptoms	1/0	0/0
Aggression	0/0	1/0
Grinding of teeth	0/0	1/0
Restless legs syndrome	0/1	1/0
Hearing problems	1/0	0/0
Memory problems	3/3	1/0
Concentration problems	0/2	0/0
Muscular complaints (weakness or tightness)	2/0	0/0
Headache	3/1	2/0
Epileptic insult	1/0	0/0
Palpitations	1/0	0/0
Auto mutilation	1/0	0/0
Pain in stomach	1/0	0/0
Neuropathy	0/0	1/0
Decreased apatite	2/0	0/0
Paresthesia	6/2	2/0
Total (serious) adverse events	58/17	38/1

Changes in mood are often followed by improvement of OCD symptoms [2]. However, OCD is a heterogenous disorder which involves multiple networks, each circuit contributing to different symptom clusters [4, 31]. Stimulation of different networks may be appropriate for different presentations of OCD. The cognitive control circuitry, involving the lateral OFC, dorsolateral prefrontal cortex (dlPFC), and dorsal anterior cingulate cortex (dACC), also plays a major role in OCD, manifesting as rigid, inflexible, and repetitive behaviors [33]. It may be possible to improve outcomes of DBS by first classifying a patient to its primary clinical profile (affective vs cognitive control) and corresponding network and consequently selecting this network as a target for neuromodulation. In that way, future studies might target specific networks by stimulating the bundles in the ALIC that run to the medial OFC (affective) or the lateral OFC, PFC, and dACC (cognitive control).

In conclusion, compared to conventional DBS, connectomic DBS for OCD does not result in more symptom reduction, but is followed by less adverse effects. The present study showed that prospective targeting of the slMFB is implementable using patient-specific DWI-images. Therefore, future patients might benefit from using tractography techniques for optimal electrode site localization.

Supplementary information is available at MP's website.

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AUTHOR CONTRIBUTIONS

Conception and design: IG, RM, LL, IO, and DD. Data/literature acquisition: IG and IO. Data/literature analysis and interpretation: IG, IO, and RM. Statistical analysis: IG, IO, and RM. Drafting the manuscript: IG. Critical revision of the manuscript: All authors. Supervision: RM, IO, GvW, and DD.

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COMPETING INTERESTS

The authors declare no competing interests.

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