An Analysis of Clinical Outcome and Tractography following Bilateral Anterior Capsulotomy for Depression

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Keywords

Capsulotomy · Anterior limb of the internal capsule · Tractography · Depression · Obsessive-compulsive disorder · Limbic system · Frontal lobes · Deep brain stimulation

Abstract

Introduction: Bilateral anterior capsulotomy (BAC) is an effective surgical procedure for patients with treatment-resistant major depression (TRMD). In this work, we analyze the connectivity of the BAC lesions to identify connectivity “fingerprints” associated with clinical outcomes in patients with TRMD. **Methods:** We performed a retrospective study of ten patients following BAC surgery. These patients were divided into “responders” and “non-responders” based on the relative change in the Beck depression inventory (BDI) score after surgery. We generated the dorsolateral prefrontal associative (DLPFC) pathways and the ventromedial prefrontal limbic (vmPFC) pathways going through the anterior limb of the internal capsule and analyzed if the overlap of the BAC lesions with these pathways was associated with either outcome. Finally, we used the BAC lesions of our patients to generate group-averaged connectivity “fingerprints” associated with either outcome. **Results:** Six patients were responders

(≥50% improvement in BDI), four patients were non-responders (<50% improvement). No significant impairments were found in most neuropsychological tests after surgery. The overlap analysis showed that in the responder group, there was less involvement of the DLPFC pathways than the vmPFC pathways ($p = 0.001$). Conversely, in the non-responder group, there was no significant difference between the involvement of both pathways ($p = 0.157$). The responder and non-responder connectivity fingerprint showed significant connections with the vmPFC limbic areas. However, the non-responder connectivity fingerprint also showed stronger connectivity to associative areas including the DLPFC and lateral orbitofrontal cortices. **Conclusions:** The optimum outcome following BAC surgery in this cohort was associated with interruption of vmPFC pathways and the relative preservation of DLPFC pathways. © 2019 S. Karger AG, Basel

Introduction

Treatment-resistant major depression (TRMD) is a major cause of significant disability and mortality. Surgical intervention can be life-saving when all conservative and medical measures have been exhausted. The recent

Table 1. Clinical and demographic data of the patients

Cases	Gender/age at surgery	Handedness	Baseline BDI	Post-op BDI	Bilateral lesion volume, mm ³
Responders					
1	F/21	R	35	7	1,119
2	F/48	R	34	4	2,395
3	F/60	R	27	6	3,861
4	F/27	R	43	6	3,820
5	F/37	R	43	18	3,027
6	F/57	R	30	15	3,287
Non-responders					
7	F/38	R	32	35	2,406
8	F/46	R	31	21	2,855
9	M/24	R	47	30	2,264
10	F/51	R	30	25	1,686

F, female; M, male; BDI, Beck Depression Inventory; Post-op, postoperative at 1 year; R, right.

Table 2. Side effects after BAC surgery presented immediately or persistently more than 12 months

Side effect	Immediate	>12 months
Confusion	3	0
Visual pseudohallucinations (spontaneous visual imagery)	1	0
Increased appetite	1	0
Decreased motivation	1	3
Decreased smell	1	0
Increased libido (persistent perineal arousal, unrelieved by orgasm)	1	0
Fatigue	1	2
Subjective emotional blunting	1	1
Difficulty forming higher order thoughts and ideas	0	2
Poor memory	1	3
Poor grooming	0	1
Headache	1	0
Burden of normality, acquired developmental deficit syndrome*	0	2
Psychomotor slowing	3	1
Facial weakness	2	0

The numbers in each cell represent the number of patients with a given side effect. * An unexpected long-term side effect was the syndrome known as the burden of normality. This is the constellation of psychological symptoms that surface as the individual adapts to being “cured” [10].

disappointing results in deep brain stimulation clinical trials for TRMD have rekindled an interest in ablative procedures for these patients [1, 2]. Bilateral anterior capsulotomy (BAC) has demonstrated long-term beneficial effects for TRMD. The results, however, are not uniformly excellent and can include side effects such as lack of motivation, fatigue, and working memory impairment [3–5]. The anterior limb of the internal capsule (ALIC) is composed of pathways from different circuits including

the dorsolateral and ventromedial prefrontal pathways corresponding to the associative and limbic circuits, respectively [6–8]. Our goal is to determine which of these pathways within the ALIC is responsible for the benefits following BAC surgery and which may be responsible for less optimal outcomes. We hypothesized that the pattern of white matter disruption by the BAC lesion would be different between patients and this may be related with the clinical outcome. In this study, we traced the dorso-

Table 3. Description of the neuropsychological tests by cognitive domain

Domain	Neuropsychological tests
Attention	Trails A, Stroop Words/Colors, WAIS-R/III Digit Symbol
Verbal memory	Rey Auditory Verbal Learning Test
Visual memory	Rey-Osterrieth Complex Figure (or alternate form, e.g., Taylor)
Phonemic fluency	Controlled Oral Word-Association Test
Semantic fluency	Animal Category Fluency Test
Abstraction	WAIS-R/III Similarities
Executive functioning	Wisconsin Card-Sorting Test, Trails B; Stroop Interference; Tinkertoy Test
Visuomotor construction	Rey-Osterrieth Complex Figure (or alternate) Copy, WAIS-R/III Block Design
Motor	Finger-Tapping Test, Grooved Pegboard Test
Behavioral rating: self and family	Frontal Systems Behavior Scale

lateral and ventromedial prefrontal pathways going through the ALIC connecting the prefrontal cortex with subcortical structures, including the thalamus and mid-brain nuclei. We analyzed the extent of damage of those pathways and its relation with the clinical outcome for each patient. Finally, we used high-quality datasets widely used in the neuroimaging community [9] to obtain the connectivity “fingerprints” of the BAC lesions associated with clinical outcomes in patients with TRMD.

Patients and Methods

The clinical research ethics board of our center approved the study and all patients provided consent. We retrospectively analyzed patients operated at our center for severe life-threatening TRMD from 2000 to 2014. The patient selection process, perioperative management, and detailed follow-up assessments have been previously reported [4]. The demographic and clinical data of the patients are summarized in Table 1. Side effects after the surgical intervention are presented in Table 2 [10]. As part of the clinical capsulotomy program, each patient undergoes comprehensive preoperative neuropsychological testing (Table 3) at 2 months and at about 1 year after surgery, with the option of repeat testing if impairments are demonstrated at 1 year. For logistical

reasons, not all patients followed this protocol. These included: no preoperative data in one patient, loss to follow-up in one patient, delay of the second testing to 2 years in one patient and 5 years in another, and missing frontal behavioral data (Frontal Systems Behavior Scale) in one patient. A change (either improved or worse) in domains is identified if there is a difference of 10 or more T-score points between preoperative and postoperative scores. The surgical procedure was performed under local anesthesia using frame-based stereotactic techniques. The location of the most inferior lesion was selected from a thin-cut T1-weighted axial magnetic resonance image (MRI) through the lowest portion of the ALIC. The target was the midpoint of the ALIC in its anterior-posterior and medial-lateral extent. Radiofrequency lesions were made with a 2.1-mm diameter, 5-mm exposed length electrode (Radionics, Burlington, MA, USA) heated to 80 °C for 60 s. Four lesions, each overlapping 1 mm, were completed in a sequentially more rostral column following the superior-lateral deviation of the ALIC in the coronal plane avoiding the nucleus accumbens, ventral putamen, and the caudate [3].

Tractography Analysis

To trace the major pathways of the ALIC, we used a high angular resolution diffusion imaging (HARDI) human template of 72 healthy subjects that matched the Montreal Neurological Institute (MNI) standard space (<https://www.nitrc.org/projects/iit/>) [11]. Fiber orientation distributions were estimated with constrained spherical deconvolution, probabilistic tractography was performed with 50,000 fibers and the rest of default parameters using the MRtrix software package (Brain Research Institute, Melbourne, Australia) [12].

The fiber tracking of the ventromedial prefrontal limbic (vmPFC) pathways was performed as follows: Seed regions of interest (ROIs): substantia nigra (SN), ventral tegmental area (VTA), and “prefrontal thalamus” defined by the thalamic connectivity atlas (FMRIB software library, Oxford, UK) [13]. Inclusion ROI: ALIC. Target ROIs: Brodmann areas 11, 12, ventromedial part of 10, and most ventral part of 25, 32 (Fig. 1a).

The fiber tracking of the dorsolateral prefrontal associative (DLPFC) pathways was performed as follows: Seed ROIs: SN, VTA, and prefrontal thalamus. Inclusion ROI: ALIC. Target ROIs: Brodmann areas 8, 9, lateral part of 10, and 46 [6, 14–20] (Fig. 1a).

To refine these pathways, we excluded from the tracking process: the posterior limb of the internal capsule, retrolenticular internal capsule, and corpus callosum. Several atlases were used to obtain the ROIs for this study [21–26].

Segmentation of the Lesions

The BAC lesions were identified on each patient’s postoperative T1-weighted MRI scans (1 mm slice thickness) taken more than 2 months after surgery. The lesions were manually segmented on StealthViz software (Medtronic, Minneapolis, USA) by a researcher unaware of the clinical outcome of the patients. We then performed brain extraction of the T1 using BET (Brain Extraction Tool, FSL v5.0) in the FSL software (FMRIB software library, Oxford, UK) [24]. To register each patient’s T1 postoperative scan to the human template based on 72 subjects, we performed a two-stage linear registration using FLIRT (FMRIB’s Linear Image Registration Tool) followed by non-linear registration using FNIRT (FMRIB’s Non-Linear Image Registration Tool) on FSL software [24, 27]. For this step, we used an aged-related atrophy template

Fig. 1. Tractography and segmentation workflow. Refer to the Methods section for a detailed description of each step. **a** The HARDI IT human template ($n = 72$) and constrained spherical deconvolution probabilistic tractography were used to trace the DLPFC and vmPFC pathways using the prefrontal thalamus and the SN/VTA as seed ROIs and DLPFC and vmPFC as target ROIs. **b** Each T1-weighted image of the patient was registered to the anatomical T1-weighted human template ($n = 72$) using the two-stage linear registration followed by non-linear transformation.

The BAC lesions were manually segmented and transferred to standard space. Overlap analysis was performed to obtain the fraction of the pathway affected by the lesion. Finally, the lesion was transferred to the native space of the NKI subjects and connectivity “fingerprints” were obtained using the BAC lesions as seed ROIs. ALIC, anterior limb of the internal capsule; HARDI, high angular resolution diffusion imaging; SN/VTA, substantia nigra and ventral tegmental area; ROIs, regions of interests; MNI, Montreal Neurological Institute standard space.

that was also normalized to the MNI space [28]. The registration was carefully inspected using several landmarks such as anterior/posterior commissure, corpus callosum, putamen, caudate, and nucleus accumbens. On visual inspection, this registration strategy was more accurate than the registration using other standard MNI templates. After these steps, we used the warp-fields to transform the segmented BAC lesions of our patients to the MNI standard space (Fig. 1b). Then, to obtain the fraction of the pathway affected by the lesion, we calculated the overlap between the BAC lesion of each patient and the vmPFC or DLPFC pathways using the Fiji software with the JACoP plugin (National Institutes of Health, Bethesda, MD, USA) [29, 30] (Fig. 1b). We used the Mander’s II

overlap coefficient, which describes the fraction of an object A (pathways) overlapping with an object B (BAC lesion) [31, 32].

Statistical Analysis

We summarized the clinical parameters and the volume of the lesions (mm^3) using mean and standard deviation. The Shapiro-Wilk normality test was performed for all variables and the data was normally distributed, therefore parametric tests were used. We calculated the clinical outcome (% of improvement) based on the Beck depression inventory (BDI) scores at baseline and at 1 year postoperatively, and the patients were divided into two groups: “responders” with $\geq 50\%$ improvement and “non-responders”

Table 4. Group analysis of each neuropsychological tests before and more than 12 months after surgery

Variable	Mean score baseline (SD)	Mean score postoperative (SD)	Significance level
Digit Span	47.0 (7.3)	49.9 (5.2)	0.132
Spatial Span	51.3 (4.3)	52.3 (7.5)	0.820
WAIS Coding	45.3 (14.4)	52.3 (9.8)	0.053
Arithmetic	47.6 (11.4)	51.0 (14.1)	0.490
Trails A	40.4 (9.5)	39.4 (8.6)	0.712
Trails B	41.1 (8.8)	46.1 (8.8)	0.258
Similarities	50.3 (7)	55.1 (9.6)	0.062
Stroop Interference	48.7 (4.4)	51.7 (9.0)	0.365
WCST (Perseverative Errors)	49.3 (9.7)	56.0 (12.1)	0.342
WCST (Non-Perseverative Errors)	49.7 (7.7)	50.9 (9.0)	0.836
RAVLT Delayed Recall	36.4 (15.7)	41.7 (11.1)	0.307
RCF Copy	40.3 (9.6)	50.1 (7.5)	0.034*
RCF Delayed Recall	33.7 (16.3)	42.1 (12.5)	0.053
COWAT (Fluency)	31.3 (10.1)	39.4 (9.6)	0.164
Animal Fluency	38.6 (18.1)	40.7 (12.0)	0.664
Block Design	47.3 (7.7)	47.1 (6.6)	0.958

*The only significant improvement was in the complex figure (RCF) copy. WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test; RAVLT, Rey Auditory Verbal Learning Test; COWAT, Controlled Oral Word Association Test.

with <50% improvement [33]. Also, we analyzed the most common normatively corrected scores for each individual neuropsychological test comparing group baseline performance to more than 12-month postoperative performance (Tables 5 and 6). We performed two-tailed paired *t* tests to compare: (1) the clinical outcome (BDI) before and after BAC, (2) the neuropsychological scores before and after BAC, and (3) the overlap coefficients within each outcome group. We also performed two-tailed unpaired *t* tests to compare the volume of the lesions between outcome groups. Significance level was set at $p < 0.05$ and we used SPSS software package 22.0 (IBM Corp., Armonk, NY, USA).

Connectivity Fingerprints

To obtain the connectivity fingerprints of the patient-derived BAC lesions associated with each outcome, we obtained the imaging data of forty-one subjects with major depression from the freely available neuroimaging community sample Nathan Kline Institute-Rockland Sample (NKI-RS) [9]. The specifications of the imaging protocol are available at http://fcon_1000.projects.nitrc.org/indi/enhanced/mri_protocol.html. All imaging data, including T1-weighted and diffusion-weighted images (DWI), were pre-processed using FSL tools and PANDA tools [34]. We used the Eddy tool to correct for Eddy current-induced distortion and subject movement [35]. High resolution T1-weighted images underwent skull stripping using BET with the threshold carefully adjusted to avoid any exclusion of the orbital brain areas. We used the DTIFIT tool for diffusion tensor imaging fitting, and BEDPOSTX tool to estimate the probability distribution of at most three fiber populations at every voxel [36, 37]. We then registered the DWI data with the anatomical T1, and with the standard MNI space using two-stage linear registration with FLIRT and non-lin-

Table 5. Frontal systems behavior scale

Case	Test interval	Apathy/ abulia	Disinhibition	Executive function
Responders				
1	12 months	+	+	+
2	12 months	+	+	+
3	7 months	na	na	na
4		na	na	na
5	12 months	=	+	-
6	5 years	na	na	na
Partial responders				
7	24 months	+	-	+
8	12 months	+	=	=
9		na	na	na
10	12 months	--	=	=

A change (either improved or worse) in domains is identified if there is a difference of 10 or more T-score points between pre-operative and postoperative scores. Case 7 had problems with inhibitory control, case 5 with executive abilities, and case 10 with apathy. Only case 10 had apathetic frontal behavior that was clinically significant. na, not available (missing data or lost to follow-up); +, improved; =, same; -, worsened; --, clinically significant worsening.

Table 6. Other neurocognitive domains

Case	Test interval	Attention	Mental speed	Verbal memory	Visual memory	Phonemic fluency	Semantic fluency	Abstraction	Inhibitory control	Problem solving	Visuomotor construction	Motor speed	Motor dexterity
Responders													
1	12 m	+	+	+	+	=	+	=	+	+	=	+	+
2	12 m	+	+	=	=	+	+	=	-	=	=/+	+	+
3	7 m	=	=	--	+	=	=	=	=	=	+	=	=
4		na	na	na	na	na	na	na	na	na	na	na	na
5	12 m	=	=	+	+	=	--	=	+	=	=	+	+
6	5 y	=	=	=	=	=	-	+	=	na	+	=	=
Partial responders													
7	24 m	=	+	+	+	+	=	+	=	=	=	+	=
8	12 m	+	+	=	=	+	+	+	=	=	=	+	=
9		na	na	na	na	na	na	na	na	na	na	na	na
10	12 m	+	+	=	+	+	=	=	=	=	=	+	=

A change (either improved or worse) in domains is identified if there is a difference of 10 or more T-score points between preoperative and postoperative scores. na, not available (missing data or lost to follow-up); y, years; m, months; +, improved; =, same; -, worsened; --, clinically significant worsening.

ear registration with FNIRT. The segmented BAC lesions of our patients in standard MNI space were transformed to the native space of each of the forty-one subjects (Fig 1b). To investigate the connectivity of the BAC lesions, whole-brain probabilistic tractograms were generated from the patient-derived BAC lesions using the PROTRACKX tool [38]. We generated 5,000 streamline samples from each voxel of the BAC lesion. The tractograms were normalized, thresholded at 95% probability of connection, binarized, and summed between subjects using fslmaths. We then created group-averaged probabilistic tractograms of the responder and non-responder group. We also generated tractograms based on the overlap or difference between both responder and non-responder maps.

Results

Ten patients with severe life-threatening TRMD were admitted to our center for BAC surgery. The mean BDI score before surgery was 35.2 (SD = 6.8) and there was a significant difference with the mean BDI score after surgery 17.9 (SD = 9.4) ($t(9) = 5.149$, $p = 0.001$). All patients reported improvements in their suicidal ideation at 1 year and maintained this until the last follow-up visit. In regards of BDI score, six patients were responders ($\geq 50\%$ improvement in BDI) and four patients were non-responders ($< 50\%$ improvement in BDI). The mean volume of the lesions was 2,672 mm³ (SD = 879.9 mm³) and there was no significant difference in the volume of the lesions between responders and non-responders ($t(8) = 0.055$, $p = 0.954$) (Table 1). Statistical analysis of the neuropsychological

results before and after surgery revealed no significant differences for any individual neuropsychological test, with the exception of significant improvement in the complex figure copy, likely representing a practice effect (Table 4). Taking into account individual patients within each outcome group, compared to the responders, the non-responders did show more frontally based behavioral difficulties (2/3 patients in the non-responder group and 1/3 patients in the responder group). Only frontal apathy in one patient was of clinical significance and this occurred in the non-responder group (Table 5). With respect to non-responders, the responders showed isolated random impairments in other neurocognitive domains including inhibitory control, verbal memory, and semantic fluency (Table 6). In Figure 2, the tractography analysis showed the white matter pathways from the thalamus to the DLPFC (associative) and vmPFC (limbic) areas (also known as anterior thalamic radiations). The pathways from the midbrain (SN/VTA) to the same cortical areas (also known as the mesocorticolimbic pathways) were also demonstrated. These pathways show a gross anatomical segregation within the ALIC: the anterior thalamic radiations were located medial with respect to the mesocorticolimbic pathways. Then, depending on its cortical targets, the vmPFC limbic pathways showed a ventromedial position in the ALIC with respect to the dorsolateral position of the DLPFC associative pathways. In the responder group, there was a significant difference ($t(5) = -8.001$, $p = 0.001$) between the involvement of the DLPFC (over-

Fig. 2. Tractography anatomy of the ALIC. Left upper panel: anterior thalamic radiations connecting the thalamus with the DLPFC associative and vmPFC limbic circuits. In the axial view, the pathways connecting the thalamus with the vmPFC (green) and the DLPFC (red) are located at the medioventral and mediodorsal aspects of the ALIC, respectively, as shown in the coronal view. * The thalamic limbic circuit encompasses the inferior thalamic peduncle (ITP), which is one of the targets of neuromodulation for depression and OCD. Left lower panel: mesocorticolimbic pathway connecting the SN/VTA with the prefrontal cortex. In the axial view, the mesolimbic pathway (green) is connecting the midbrain nuclei with the vmPFC and the mesocortical pathway (red) is connecting midbrain nuclei with the DLPFC. In the coronal view, the

mesolimbic pathway (green) arrives at the lateroventral aspect of the ALIC and the mesocortical pathway (red) at its laterodorsal aspect. * The mesocorticolimbic pathways encompasses the medial forebrain bundle (MFB), which is a target of neuromodulation for TRMD. Right panel: based on the cortical targets, the DLPFC and vmPFC pathways showed a dorsoventral segregation. The vmPFC pathways (green) are ventromedial to the DLPFC pathways (red). * The vmPFC limbic pathway is also related with the ventral striatum/ventral capsule (VS/VC), which is another well-known target for TRMD and OCD. The background image was obtained from the BigBrain project (<https://bigbrain.loris.ca/main.php>) [77].

lap coefficient = 0.05, 95% CI = 0.03–0.06) and vmPFC pathways (overlap coefficient = 0.12, 95% CI = 0.08–0.15). In contrast, in the “non-responder” group, there was no significant difference ($t(3) = -1.877$, $p = 0.157$) in the involvement of DLPFC (overlap coefficient = 0.07, 95% CI = 0.03–0.12) and vmPFC pathways (overlap coefficient = 0.11, 95% CI = 0.07–0.15). Finally, we found the connections that were disrupted by the lesions of both outcome groups. The connectivity fingerprints of the responders showed significant connections with limbic areas such as vmPFC, and the anterior part of the subcallosal cingulate cortex (SCC), and the amygdala. The connectivity fingerprints of the non-responders showed similar connections with the limbic areas as the responder group but more significant connectivity with the DLPFC and lateral orbitofrontal cortex and less connectivity with the SCC than the responder group (Fig. 3).

Discussion

We analyzed the connectivity of the lesions of ten patients with TRMD who had undergone BAC at our center. We confirmed the topography of the ALIC according to previous anatomical descriptions with the vmPFC limbic pathways being ventromedial to the DLPFC associative pathways (Fig. 2). The trajectory of these pathways also encompassed other white matter targets used in neuromodulation for TRMD and obsessive-compulsive disorder (OCD) including the inferior thalamic peduncle, medial forebrain bundle, and ventral capsule/striatum [39–46] (Fig. 2). This finding suggests that other surgical approaches are targeting the same circuit for depression that we described in this study. Moreover, we found that each lesion had slightly different degrees of involvement of the pathways of interest. This may be re-

Fig. 3. Connectivity “fingerprints” of the BAC lesions associated with clinical outcomes. These probabilistic maps showed the pathways disrupted by the BAC lesions. **a** The connectivity fingerprint of the responder group showed significant disruption of the connections between the subcortical nuclei (thalamus and midbrain) and the vmPFC areas including Brodmann areas 11, 12, and most ventral part of 32 (arrows). **b** The connectivity fingerprint of the non-responder group showed significant disruption of the similar pathways as the responder group but with less connectivity with

the SCC (arrow in axial view). **c, d** In the responder group (**c**), the disruption of the DLPFC pathways was notably less (arrows) than in the non-responder group (**d**). **e** The overlap map (yellow) between groups showed disruption of the vmPFC (green cortical areas) and little disruption of the DLPFC (red cortical areas). **f** The difference map (yellow) between responder and non-responder groups showed the significant disruption of the DLPFC (red cortical areas).

lated to minor differences in tissue responsiveness to thermal damage [47] or slight variations in surgical technique between patients. We found, in the responder group, significantly less disruption of the DLPFC pathway compared with the vmPFC pathway. Furthermore, the connectivity “fingerprints” showed that non-responders had more significant disruption of the DLPFC pathways and less significant disruption of the SCC than the responder group.

Depression not only involves sadness and suicidality but also disturbances in neurocognition and neurovegetative functions such as sleep, weight, appetite, energy,

libido, and demoralization. Demoralization in depressive illness is a negative and pessimistic mindset that stems from the consequences of a chronic mental disorder that has resulted in lost opportunities, compromised coping skills and functioning, social isolation, and dependency on others [48]. The patients with significantly less disruption of their DLPFC pathways were able to maximally improve their depression more than 50%. Four of the six responders even became remitters (BDI <9) [33]. The DLPFC is the cortical node for one of several frontal-subcortical circuits. The DLPFC-subcortical circuit is responsible for “executive functions,” which consist of

three core neuropsychological abilities: inhibitory control, working memory, and cognitive flexibility [49, 50]. As can be seen from Tables 4–6, the vast majority of neuropsychological domains were generally preserved or improved after BAC. Frontal behaviors, the domains at greatest risk given the location of the lesion, were mostly unchanged or improved. The neuropsychological metrics that reflect frontal lobe function are, however, neither robust nor consistent and this may be because executive functions such as cognitive flexibility are not easily captured on formal neuropsychological testing. However, it is anticipated that with loss of cognitive flexibility, patients may find it harder to reverse the demoralization that accompanies chronic severe depression and this may account for the poorer clinical outcomes in the non-responder group. Based on our findings, we postulate that the “ideal” BAC would disrupt the vmPFC limbic pathways responsible for sadness and suicidality while preserving the DLPFC pathways.

The pathophysiology of depression has been related to the interaction between the DLPFC associative and vmPFC limbic circuits [51, 52]. Different cortical areas of the limbic circuit included in the vmPFC have been suggested as the origin of depression [51, 53, 54]. These findings are supported by other studies where patients with lesions in the vmPFC showed relative resistance to depression, whereas patients with lesions in the DLPFC presented with depressive symptoms more frequently [55]. Multiple overlapping lines of evidence have shown that the brain region of the vmPFC that best correlates with depression is the SCC [56–61]. The SCC is a major component of the limbic system which has long been held responsible for normal emotional function [62, 63]. In depression, there appears to be an inverse relation of activity between the SCC and the DLPFC such that increased activity in the SCC is associated with decreased activity in the DLPFC and that this pattern of activity reverses with treatment response [58–60, 64, 65]. Structurally compromising the DLPFC by interrupting more dorsal fibers in the ALIC may compromise this adaptive inversion and result in worse outcomes after BAC surgery [59]. This reciprocal relationship between limbic and associative circuits provides a functional explanation for the findings that our patients who did poorer after BAC have had more injury to the DLPFC associative circuit because of the more dorsal extension of their lesions.

BAC is one of the known ablative procedures used in psychiatry to treat either TRMD or treatment-resistant OCD. To achieve optimal results and to avoid unwanted adverse effects, it is important to know the specific white

matter pathways that should be interrupted by the lesion. To date, these are unknown. Moreover, there is currently no clear consensus on the “ideal” BAC lesion size or its dorsal-ventral extent. Within the ALIC, there are no obvious anatomical landmarks to guide lesion location or its size. The size of the lesion has been based on each center’s clinical experience [3–5, 66]. The measurement of the lesion at our center has been 5.2 mm in width (range 2–8 mm) and 14.6 mm in height (range 11–16 mm), which is narrower and shorter than the Dundee and Stockholm capsulotomies (8 mm in width and 18–20 mm in height) [3, 67]. Some authors have found that deeper lesions are associated with better clinical outcomes [5] and smaller lesions with fewer adverse effects [68]. Therefore, the trend is to target the more ventral aspects of the ALIC [69, 70]. Our work supports this trend and provides evidence that the best clinical results were associated with lesions selectively affecting vmPFC pathways in the ventromedial aspect of the ALIC with relative preservation of the DLPFC pathways in the dorsolateral part of the ALIC. We also found that advanced fiber tracking techniques can distinguish between the DLPFC pathway and the vmPFC pathway within the ALIC as others have also found [71–73]. Although there was some degree of overlap, we segregated the associative and limbic circuits with a regional difference that could be useful in the surgical planning for lesioning or neuromodulation.

The main limitations of this work are the small sample size and the retrospective nature of the analysis. Moreover, tractography analyses have inherent limitations related to distortion, registration, and processing issues as reported elsewhere [74, 75]. Another limitation is that the analysis was performed on DWI data of other depressed subjects using the lesions of our patients. However, the advantage of this approach is the use of high-quality data acquisition, which is essential to obtain accurate and meaningful representations of the white matter pathways in regions with complex fiber configurations. Furthermore, to increase the sensitivity of tractography in detecting regional differences, we traced the connections seeding from subcortical nuclei to larger cortical areas rather than specific Brodmann areas as has been done in other studies [73]. In this work, we provide more evidence that tractography would aid in the identification of brain circuits in major depression. This would help to create patient-specific targets in order to improve outcomes and minimize side effects [32, 76].

Conclusion

The optimal clinical outcome following BAC surgery in our cohort was associated with the interruption of vmPFC limbic pathways and the relative preservation of the DLPFC pathways. We postulate that the interruption of the vmPFC limbic pathway may be related with the immediate suppression of sadness. The recovery from the depressive syndrome is slower and might depend in part upon preserving the DLPFC associative pathway. Further prospective studies with larger sample sizes will be needed to confirm these findings. We suggest that tractography might be helpful to prospectively identify those pathways within the ALIC that need to be disrupted or preserved during BAC.

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