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Ablative Limbic System Surgery: Review and Future Directions

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Abstract The limbic system is a network of interconnected brain regions regulating emotion, memory, and behavior. Pathology of the limbic system can manifest as psychiatric disease, including obsessive-compulsive disorder and major depressive disorder. For patients with these disorders who have not responded to standard pharmacological and cognitive-behavioral therapy, ablative surgery is a neurosurgical treatment option. The major ablative limbic system procedures currently used are anterior capsulotomy, dorsal anterior cingulotomy, subcaudate tractotomy, and limbic leucotomy. In this review, we include a brief history of ablative limbic system surgery leading up to its current form. Mechanistic justification for these procedures is considered in a discussion of the pathophysiology of psychiatric disease. We then discuss therapeutic efficacy as demonstrated by recent trials. Finally, we consider future directions, including the search for predictors of treatment response, the development of more precise targeting methods, and the use of advances in neuroimaging to track treatment response.

Introduction

The limbic system plays a major role in the regulation of emotion, memory, and behavior [1]. Originally described by Papez in 1937 [2] and further characterized by MacLean in the early 1950s [3], the limbic system is currently understood to include subcortical structures (such as the hippocampus, amygdala, and ventral striatum) and cortical structures (including the orbitofrontal cortex, cingulate cortex, and insula) [1]. The past decades have brought a refinement in functional understanding of limbic circuits. One current model of the limbic system includes multiple subcircuits, including hippocampal-diencephalic and parahippocampal-retrosplenial networks mediating memory and spatial orientation, and a temporo-amygdala-orbitofrontal-cingulate network broadly involved in emotion and its link to behavior [1]. The complex neuroanatomy of the limbic system parallels its requirement to support these diverse functions.

Because of its complex structure and function, the limbic system is uniquely vulnerable to dysfunction, which can manifest behaviorally as neurological or psychiatric diseases. At their conceptual core, these disorders are characterized by a variety of emotional, attentional, and behavioral perturbations, functions that are governed by the limbic system. Obsessive-compulsive disorder (OCD), major depressive disorder (MDD), and bipolar disorder, among many others, are all

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psychiatric disorders with increasingly well-understood mechanistic underpinnings in limbic system dysfunction.

The majority of patients with these disorders improve with traditional pharmacological and cognitive-behavioral therapies. However, in both OCD and MDD, about 10–20 % of patients do not respond adequately to these conventional approaches [4–7]. For these refractory patients, neuromodulatory surgical procedures, including stereotactic ablative lesions and deep brain stimulation, can be effective treatment options. The goal of this review is to discuss this first category of procedures, ablative lesions, which are believed to disrupt dysfunctional networks implicated in disorders of the limbic system. Here we will briefly discuss the history of ablative limbic system surgery through its initial implementations, then focus on the current utilizations of and trends in cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leucotomy. In doing so, we will discuss the pathophysiological circuits in disorders of the limbic system that motivate the use of these procedures, the studies defining that pathophysiology, and future directions for limbic system surgery.

History

In 1891, Burckhardt published the results of a series of six resections of the left frontotemporal cortex in patients with various psychiatric disorders [8]. Primate studies implicating the frontal lobe in behavioral pathology by John Fulton inspired Egas Moniz's development of the prefrontal leucotomy in the 1930s, in which the frontal white matter was surgically interrupted [9]. In this era before antipsychotic drugs, patients with severe psychiatric disease such as schizophrenia had few options outside of overcrowded asylums. For some of these patients, Moniz's procedure provided symptomatic relief and the possibility of moving on from lifelong psychiatric institutionalization. It was seen as a remarkable accomplishment for a challenging situation, and, in 1949, Moniz was awarded the Nobel Prize in Physiology or Medicine [10]. Moniz's accomplishment was particularly noteworthy because it underscored the emerging understanding that psychiatric diseases have an anatomical and functional basis in the brain.

In the 1940s, Freeman and Watts adapted Moniz's procedure to a technically simpler procedure that could be performed through burr holes, terming it the "lobotomy." Freeman eventually further simplified the technique to a transorbital procedure that could be performed at the bedside, totaling approximately 20,000 procedures by 1951, without neurosurgical support or backup [11]. Again, therapeutic efficacy was seen for some patients, but its use became increasingly indiscriminate, and many patients were neurologically devastated. The advent of antipsychotics in the early 1950s led to a marked decrease in the use of the lobotomy.

Why did these procedures provide benefit for some patients? Broadly speaking, the interruption of pathological frontolimbic circuits is likely what mediated symptomatic improvement. Analysis of historical lesions, limited as it is without contemporary imaging, has identified damage to many of the same mediobasal frontal structures and pathways included in modern lesions [12, 13]. The procedures in the 1940s and 1950s were performed without the benefit of stereotaxy or radiography and were therefore heterogeneous, imprecise, and difficult to study, and often associated with major neurological morbidity [14]. However, it was noted that those procedures that featured smaller lesions without major cortical destruction could be effective in the treatment of psychiatric disease while sparing neurological function [15•]. At around the same time, the advent of stereotactic techniques made it possible to safely and reproducibly create lesions, with minimal anatomical disruption [15•].

Stereotaxis: The Advent of Target Definition

In the early 1900s, Horsley and Clarke pioneered the development of stereotactic procedures, in which a rigid head-mounted frame is adjusted in the Cartesian x, y, and z planes to target a specific location in the brain [16]. In 1947, Spiegel and Wycis were the first to apply the "Horsley apparatus" to humans when they performed a stereotactic medial thalamotomy [17], which was intended as a treatment for a patient with intractable "emotional reactivity." Today's stereotaxy has improved over the decades since Spiegel and Wycis' plaster-and-metal frame, providing increasingly precise and targeted means of creating reproducible lesions in a minimally invasive manner.

Stereotaxy is one of numerous technical advances since the 1940s that have made psychiatric neurosurgery safer and more effective. Advancement in the understanding of the pathophysiology of psychiatric disease has also been a major development. Thus, before discussing the major ablative neurosurgical procedures for limbic system pathology, we provide an update on the circuits involved in psychiatric disease. While these targets were identified and refined by trial and error, we advance the rationale for currently utilized targets based on the current understanding of the pathophysiology of refractory OCD and depression. Initially, we focus on the role of cortico-striato-thalamo-cortical (CSTC) loops and how, when dysfunctional, their interruption may be therapeutic.

Brain Circuits Targeted by Ablative Limbic Surgery: The CSTC Loops

CSTC circuits are classically described as "loops" that bind together regions of the cortex, basal ganglia, and thalamus subserving related functions, such as movement, memory, or behavioral regulation [18]. As described by Alexander, DeLong, and Strick, there are a number of circuits projecting from the cortex to the striatum to the thalamus back to the cortex, although their exact number, as well as the functional rigidity of their boundaries, is under debate [19]. One circuit, involving the dorsal anterior cingulate cortex, orbitofrontal cortex, ventral striatum, mediodorsal thalamus, and subcortical structures such as the hippocampus and amygdala, integrates the limbic system, basal ganglia, and frontal circuits in a feedback-dependent manner to regulate behavior, specifically its affective and cognitive components [20–22] (Fig. 1a). Dysfunction within the limbic loop may therefore result in
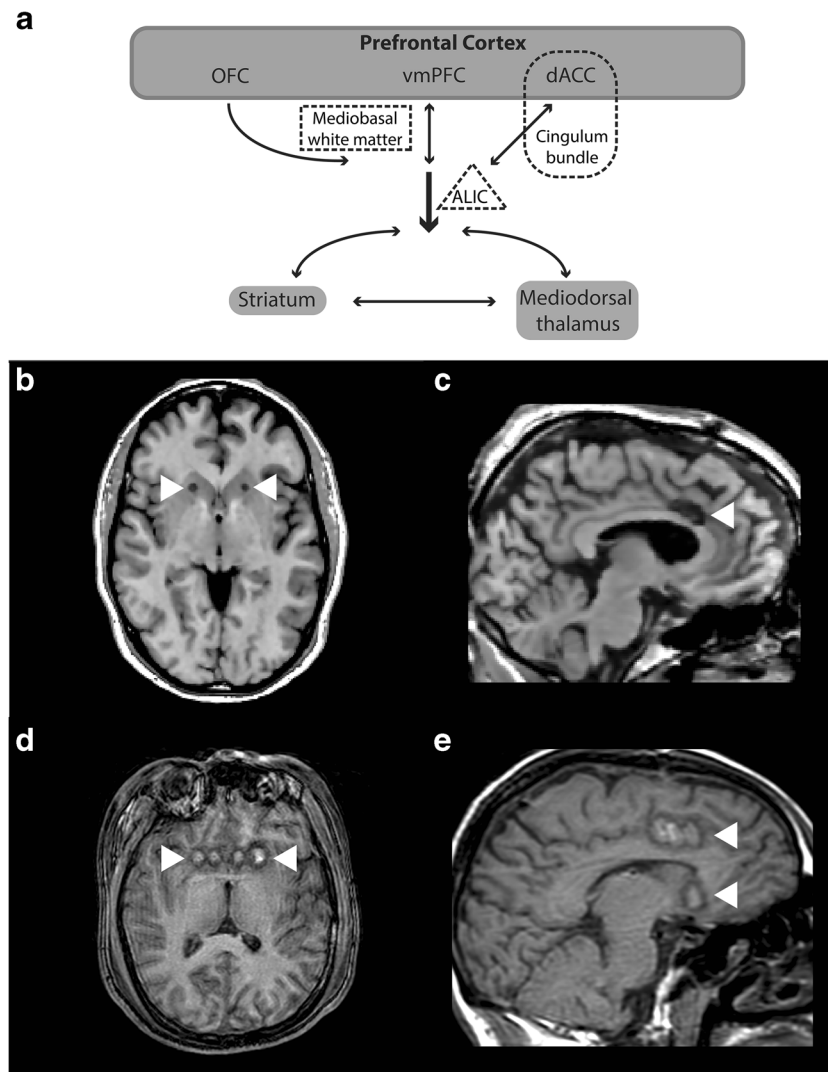

Fig. 1 Schematic of the limbic loop of the cortico-striato-thalamo-cortical (CSTC) circuits with representative T1-weighted MR images of the major ablative limbic system surgeries. Like other CSTC circuits, the limbic CSTC loop consists of input from the cortex to striatum, from the striatum to thalamus, then from the thalamus back to cortex (a). There is also involvement of subcortical limbic structures such as the amygdala and hippocampal formation (not shown). The prefrontal cortex components of the limbic CSTC loop are the orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC), and dorsal anterior cingulate cortex (dACC). These cortical structures communicate reciprocally and also send projections through the anterior limb of the internal capsule (ALIC) to the mediodorsal thalamus and striatum. Three major lesion locations for ablative limbic system surgery are shown in dashed outlines. Respective MR images are shown with white arrowheads indicating lesion location. Anterior capsulotomy (b, MRI at 6 months post-op) is performed by lesion of the ventral aspect of the anterior limb of the internal capsule (dashed triangle). Dorsal anterior cingulotomy (c, MRI at 12 months post-op) is performed by lesion of the dACC and its corresponding white matter tract, the cingulum bundle (dashed round rectangle). Subcaudate tractotomy (d, MRI immediately post-op) is performed by lesion of the mediobasal white matter (dashed rectangle). Limbic leucotomy (e, MRI immediately post-op) is a combination of dorsal anterior cingulotomy and subcaudate tractotomy

aberrant affective and cognitive processing of stimuli (the nature of that aberrance dependent on the exact disorder), resulting in abnormal behavior. The limbic loop of the CSTC circuits is therefore implicated in a number of the psychiatric disorders that limbic system modulation attempts to relieve [21, 23, 24].

Indeed, appreciation of the CSTC framework has informed the study of the anatomic and functional underpinnings of many psychiatric disorders. Functional and metabolic neuroimaging of OCD, for example, has identified dysfunction in a number of regions characterized as part of CSTC loops. Hyperactivity of the orbitofrontal cortex (OFC) [19], dorsal anterior cingulate cortex (dACC) [25], caudate [26], and thalamus has been described [27], with demonstrable decreases in metabolism on PET after treatment [28]. Symptom provocation neuroimaging studies of OCD patients have demonstrated increased OFC and ACC activity with trigger stimuli for OCD behavior [29, 30]. Finally, hyperconnectivity within CSTC circuit regions has been seen in the OFC, dACC, thalamus, and striatum [31], although pathological hypoconnectivity has also been reported [19]. The concept underlying ablative surgery for OCD is thus based on this pathological hyperactivity and dysfunctional connectivity within the limbic CSTC loop.

Other psychiatric disorders for which ablative limbic system surgery has been utilized also exhibit limbic CSTC-related dysfunction. Affective disorders, such as major depressive disorder (MDD) and bipolar disorder, have been explained in the context of dorsal, ventral, and modulatory components consisting of integrated rather than segregated CSTC circuits [15•, 32]. According to one such account, the ventral component controls affect by encoding emotional salience through the subgenual cingulate cortex, OFC, and insula, with reciprocal connections to anterior and mediodorsal thalamic nuclei through the ventral striatum. This component is typically found to be hyperactive in functional neuroimaging studies of affective disorders [33]. The dorsal component, on other hand, has been shown to mediate cognitive and motor aspects of behavior, and consists of the dACC, dlPFC, and premotor cortices, with connections to the anterior and mediodorsal thalamic nuclei through the dorsal striatum. This component has demonstrated hypoactivity in neuroimaging studies of MDD, which may partly explain the affective blunting observed in some forms of the disorder [15•]. Finally, the modulatory component, comprised of the pregenual ACC, amygdala, and the hypothalamic-pituitary axis, appears to modulate dorsal and ventral components. Though the exact method of framing CSTC circuit involvement may be different, the existence of pathological activity within associated brain regions is evident in psychiatric disease.

We now consider each of the major ablative limbic system surgeries in turn, with considerations of surgical technique, applications, and further pathophysiologic discussion.

Anterior Capsulotomy

Following Spiegel and Wycis' use of stereotaxy in humans, Leksell and Talairach developed the anterior capsulotomy in 1949 [34]. This procedure targets the ventral aspect of the anterior limb of the internal capsule (ALIC) bilaterally (Fig. 1b). Disruption of this white matter structure is thought to have provided at least some of the therapeutic relief of early lobotomies [15•]. Since then, studies of this ventral ALIC target have demonstrated orbitofrontal cortex (OFC) and subgenual cingulate projections traveling to medial thalamic nuclei [15•].

Capsulotomy is currently performed with either radiofrequency thermoablation or stereotactic radiosurgery. The latter, often performed using the Gamma Knife device ("gamma capsulotomy"), is growing in popularity recently due to its less invasive nature [35] and amenability to randomized, blinded trials [36•]. Capsulotomy has been studied in OCD, in which symptom improvement for OCD is typically measured by decreases in scores on the Yale-Brown Obsessive Compulsive Disorder Scale (Y-BOCS) [37]. Using this scale, a "full" response to treatment is typically defined as a ≥35 % decrease in score from baseline. "Partial" response is typically defined as a decrease of 25–35 % from baseline Y-BOCS score. A recent retrospective analysis of 19 patients treated over a decade with thermoablation found that 36.8 % were full responders and 10.5 % were partial responders [38]. Other reports of response rate range from 48 to 80 % [39–42] (Table 1). Thermoablative capsulotomy has also been used for intractable MDD and mood disorders. A prospective study of 20 MDD patients undergoing capsulotomy over a period of 7 years demonstrated marked improvement in 55 % of patients [43]. Adverse effects in all studies of thermoablative capsulotomy can be categorized as short term vs. long term, and minor vs. serious. Serious adverse events, which are becoming increasingly less common, include hemiplegia and deficits in executive function and cognition [38]. The large majority of reported adverse events tend to be minor and short term, including asymptomatic intracranial hemorrhage, abulia, and weight gain [40, 43].

Gamma capsulotomy was first used in 1976 [47] and has seen increasing use over the last several years. The first blinded, sham-controlled, randomized controlled trial of gamma capsulotomy for refractory OCD was recently published [36•]. As in thermoablative capsulotomy, the ventral aspect of the ALIC was targeted. Of eight patients undergoing the procedure, three responded within 12 months and two more responded within 54 months (response defined by >35 % improvement of Y-BOCS score). None of the sham patients responded. Four patients within the sham group elected to undergo gamma capsulotomy in the open-label follow-up period after removal of blinding, two of whom responded. A recent retrospective study assessed gamma capsulotomy for

Table 1 Summary of major studies of ablative limbic system procedures

Procedure	Study	Sample size	Disorder treated	Mean time of LFU	Mean % change[a]	Adverse events
Anterior capsulotomy (thermoablative)	Zhan et al. [42]	53	OCD	12	−73.7	S: Memory impairment (13), UI (11) L: Personality change (3), hypersexuality (3)
	D'Astous [38]	19	OCD	84	−32	S: Frontal syndrome (5), hemorrhage (3) L: Hemiplegia (1), cognitive deficits (1)
	Hurwitz [44][b]	8	MDD	24	−57.4	S: Confusion (2), akinetic mutism (1) L: Executive dysfunction (1), fatigue (1)
	Christmas [43][c]	20	MDD	84	−50.7	S: Confusion (5), HA (3), UI (3) L: Amotivation (4), weight gain (3)
	Liu [41]	35	OCD	36	−79.2	S: UI (3), intracerebral hematoma (1) L: Apathy, abulia (2)
	Rück [45]	25	OCD	33.5	−52.5	S: Weight gain (mean 6 kg/1 year) L: UI (2), apathy (1), disinhibition (1)
	Oliver [39]	15	OCD	24	−39	S: Hallucinations (1), seizure (1) L: Behavioral disorder (1)
Gamma capsulotomy	Lopes [36•]	16	OCD	12	−51.9	S: Weight gain (4), HA (4), manic episodes (2) L: Brain cyst (1), drug abuse (1)
	Sheehan [54]	5	OCD	22	−50	None reported
	Kondziolka [48]	3	OCD	42	−54	None reported
	Lopes [46]	5	OCD	48	−36	S: HA, nausea L: Weight gain
Dorsal anterior cingulotomy	Sheth [66•][d]	64	OCD	63.8	−28	S: Memory deficit (5), abulia (4), UR (2) L: Suicide (2), infection (1)
	Shields [14][b]	33	MDD	30	−20.8	S: UI (4), memory deficit (1), infection (1)
	Jung [67]	16	OCD	24	−48	None reported
	Kim [68]	14	OCD	12	−36	S: Insomnia (4), weight change (4), HA (3)
Limbic leucotomy	Cho [80][b]	16	Bipolar	84	−40.6	S: Wound infection (1), hallucinations (1), extrapyramidal symptoms (1)
Subcaudate tractotomy	Bourne [81][e]	11	OCD	50	−42	S: Abulia (3), memory deficit (1)

LFU last follow-up (months), *S* short term, *L* long term, *UI* urinary incontinence, *UR* urinary retention, *HA* headache

[a] % change refers to % change on a given behavioral scale between preoperative administration and LFU administration. For all OCD studies, Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was used. See notation for other studies. Conventionally, 35 % change is regarded as a full treatment response

[b] Used Beck Depression Inventory as behavioral scale

[c] Used HRSD-17 as behavioral scale

[d] Includes patients from Baer et al., 1995 and Doughery et al., 2002

[e] Subcaudate tractotomy was performed as a follow-up for cingulotomy nonresponders, effectively producing a limbic leucotomy. Given the relative paucity of studies of rigidly tested patients who have undergone subcaudate tractotomy, we present these results for completeness

refractory OCD in five patients. Four of these patients demonstrated "marked clinical improvement" at a median of 24 months follow-up. Another study of three patients found that all responded to gamma capsulotomy [48]. Adverse events are similar when comparing the two capsulotomy techniques. Although the gamma capsulotomy procedure itself is relatively noninvasive, the impact of ionizing radiation must be considered. The high doses of radiation required for these procedures can lead to the development of cystic changes in the brain [36•], as well as a slightly increased risk of secondary malignancies [49]. Cognitive events were also seen, including

a manic episode in patients with previous hypomania, the development of drug abuse in one patient, and insomnia [36•].

Neuroimaging findings in patients who have undergone capsulotomy have confirmed and extended theories about hyperactivity in cortical and subcortical areas in psychiatric disease, providing valuable information about pathophysiological circuits. A recent PET study of 13 patients who had undergone capsulotomy for OCD confirmed metabolic changes in previously described areas, including the subgenual cingulate cortex, caudate, and dACC [50, 51]. These structures all have corresponding fibers that travel through the ALIC, providing

further support for a ventral ALIC target. Structural studies have noted post-operative changes in brain volume, including decreases in the ALIC, ventral striatum, thalamus, and occasionally hippocampus [52]. Another study noted novel post-operative white matter changes at 2 months after capsulotomy in five patients, which included increases in T1 signal potentially signifying axonal change [53]. Longer term studies are needed to better characterize the relationship between structural changes and clinical response. These findings will inform design of future interventions for refractory psychiatric disease.

Summary and Future Directions

Anterior capsulotomy has demonstrated efficacy for refractory OCD and mood disorders. Techniques for gamma capsulotomy, which offers the benefit of noninvasiveness, continue to be refined. Moreover, as it is the only ablative surgical modality for psychiatric disease for which a blinded trial has been performed, gamma capsulotomy has the strongest evidence supporting it. Recent trends in gamma capsulotomy include a reduction in radiation dose from 180 to 140–160 Gy and a reduction in the number of isocenters used [54]. Older studies typically delivered three bilateral doses, whereas a recent study used just one bilateral dose [54]. If similar therapeutic benefit can be achieved with less radiation, adverse events will decline as well. Moreover, further investigation is needed to determine the typical time course of response to gamma capsulotomy. In particular, time to symptomatic relief varies between individuals and studies, but typically tends to follow on the order of months to over a year. In one study, two patients who did not initially respond were considered responders at two-year follow-up [36•]. Moreover, the durability of the response to capsulotomy has not been clearly defined in the literature. Long-term follow-up studies will be needed to address these questions. Transcranial focused ultrasound (tFUS) has recently been advanced as a promising new technique for creating intracranial lesions [55, 56]. It has been used for OCD [57], but similar long-term studies are needed to better understand its efficacy and long-term potential.

Dorsal Anterior Cingulotomy

Cingulotomy was first proposed in the 1950s by Fulton and subsequently refined and popularized by Ballantine [9, 58]. In dorsal anterior cingulotomy, the anterior cingulate cortex and the cingulum bundle are ablated with stereotactic guidance (Fig. 1c). The ACC is a region within the medial prefrontal cortex consisting of the anterior aspect of the cingulate cortex as it wraps around the rostral corpus callosum [59]. It is subdivided into rostral and dorsal ACC (rACC and dACC)

regions. In broad terms, these regions appear to have emotional and cognitive functions, respectively. The ACC is known to have extensive connectivity with dorsolateral prefrontal, orbitofrontal, primary premotor, and insular cortices, along with thalamic nuclei, especially the mediodorsal thalamus. This complex connectivity enables the ACC to play a role in cognitive control [60, 61], pain [62, 63], and emotional processing [64]. Though it was commonly thought that the rostral and dorsal anatomic subdivisions represented distinct functional units, recent analysis instead suggests functional integration across these regions [65].

This combination of cognitive and emotional processing makes the ACC a theoretically ideal focus of therapeutic intervention for psychiatric disorders in which these processes are impaired. Several disorders have been treated with cingulotomy, including treatment-refractory OCD, MDD, and chronic neuropathic pain [9, 15•]. Cingulotomy lesions are typically made via radiofrequency thermocoagulation under stereotactic guidance. Though it is the most commonly used psychiatric neurosurgical procedure in the USA and Canada [15•], it is still not widely performed. However, a relatively concise literature suggests it is safe and effective in the treatment of OCD and depression.

Studies of the effectiveness of cingulotomy are relatively small but roughly uniform in results. A recent retrospective study with a cohort of 64 patients who had undergone cingulotomy for refractory OCD showed a full response rate of 47 % and partial response rate of 22 % after mean follow-up of over 5 years [66•]. Other studies of cingulotomy for OCD have described response rates of 48 % after 2 years [67], 43 % after 1 year [68], and 5 of 7 (71 %) patients after 1 year [69] (Table 1). Mood disorders show a similar response rate, with a recent study of anterior cingulotomy for intractable MDD in 33 patients showing 41 % improvement and 33 % partial improvement after 30 months [14].

Adverse events can again be categorized as short term vs. long term and minor vs. serious. Recent studies have demonstrated some short-term adverse events, but far fewer long-term adverse events. Adverse events in both categories are typically minor. One study reported the development of long-term post-operative epilepsy that required medication control [70]. Reported short-term adverse events include both urinary retention [66•] and urinary incontinence [9, 71]. Short-term cognitive changes can also occur, including blunted affect, abulia, and post-operative amnesia; these usually resolve within days [59]. Some impairment in performance on cognitive interference tasks, such as the Stroop test and Multi-Source Interference Task (MSIT) [72], have been reported in the months following cingulotomy, although these tend to resolve fairly rapidly as well [59, 73].

Similar to anterior capsulotomy, studies suggest that it takes time for the efficacy of cingulotomy to develop. In most studies, it takes from months to over a year for therapeutic

response. In one study, for example, nearly half of patients who eventually exhibited response to cingulotomy did not show appreciable symptomatic improvement for multiple follow-up visits [66•]. Mechanistically, this delay suggests potential long-term plasticity measures required for symptomatic improvement. Response appears to be durable, as the same study demonstrated long-term maintenance of response status [66•].

Summary and Future Directions

Dorsal anterior cingulotomy is thus an efficacious procedure for the treatment of refractory psychiatric disease. However, further work remains to be done in regard to defining optimal targets. dACC function continues to be investigated, and the current emerging picture of this region's functionality is an overlap in the processing of cognitive control, negative affect, and pain [65]. Indeed, the dACC of different patients with psychiatric disease may be differentially affected, leading to heterogeneous manifestations of disease and similarly heterogeneous optimal therapeutic targets. Through advances in neuroimaging combined with empirically observed symptomatic changes, further narrowing of lesion extent may be possible on an individualized basis. Moreover, despite evidence for the clinical benefit of cingulotomy, a number of questions remain about patient selection, predictors of response, and mechanism of action. Potential anatomic predictors of response were recently described, including gray matter partial volume in the dACC, as well as asymmetry of CSTC connectivity [74]. These types of neuroimaging studies will also be helpful in clarifying the mechanism of action of these procedures, which may involve changes in CSTC circuits that develop over time.

Subcaudate Tractotomy

The subcaudate tractotomy (SCT), first reported in 1960 by Knight [9], is a procedure with similar principles and indications as capsulotomy and anterior cingulotomy. Lesions are made in the frontal mediobasal white matter, which is located ventral to the head of the caudate nucleus and contains corticothalamic fibers [9, 15•] (Fig. 1d). Although the target is precisely defined in the modern era using stereotaxy, retrospective data on SCT lesions has suggested that there may be substantial patient-to-patient variation in anatomy in this brain region. A recent analysis of SCT procedures showed variable involvement of the uncinate fasciculus, medial orbitofrontal cortex, and nucleus accumbens [75].

SCT as a stand-alone procedure is not commonly used in the USA and is only slightly more popular in England [9]. In the past, it has been used for both mood and anxiety disorders, including MDD and OCD. A study of 23 patients with affective disorders demonstrated symptomatic improvement but significant cognitive changes on post-operative neuropsychological testing [76].

Despite its limited clinical use, SCT has had scientific value in its contribution to anatomic understanding of relevant pathways. Recent tractographic analyses of OFC-related white matter tracts in nonhuman primates [77] and healthy humans [78] have shed light on the anatomic organization of OFC subdivisions projecting to the thalamus and brain stem. Building on these characterizations, a similar study of OCD patients who had undergone SCT recapitulated these findings and found that the best clinical outcomes may be associated with a target in the ventral aspect of medial OFC white matter tracts [12]. This study proves, in principle, the ability of current modalities to localize an optimal target along a white matter tract for therapeutic relief, and can in theory be applied to more psychiatric disorders.

Limbic Leucotomy

Performed since the 1970s with demonstrated efficacy for mood disorders and OCD [79, 80], the limbic leucotomy is a combination of anterior cingulotomy and subcaudate tractotomy. Depending on the clinical context, the limbic leucotomy can be performed as one procedure, in which frontothalamic white matter tracts are lesioned in the basal medial frontal lobes, along with a lesion of the dACC as described above for anterior cingulotomy [9] (Fig. 1e). Alternatively, it can be performed by following up an anterior cingulotomy with SCT. One group performing the latter demonstrated a 73 % rate of symptomatic improvement in patients with OCD and intractable MDD who did not initially respond to anterior cingulotomy [81]. Another group released a 7-year prospective study of patients who received limbic leucotomy in one procedure for intractable bipolar disorder, and found a significant and stable decrease in depressive, but not manic symptoms [80].

Side effects of limbic leucotomy appear to be short term and spontaneously resolving, and include transient hallucinations, amnesia, and mania. Notably, however, abulia appears to develop at a greater rate following limbic leucotomy than cingulotomy [66•], but is still typically self-limited. Long-term adverse events include extrapyramidal symptoms treated with medication [80].

Future Directions

Over its 60-year history, ablative limbic system surgery has appeared to be an efficacious intervention for refractory psychiatric disorders. However, a number of clinical and

scientific questions have not been answered. Three major questions, in particular, deserve mention:

(1) Do neuroimaging features or other biomarkers exist that predict clinical response?
(2) What is the mechanism of efficacy of ablative limbic system surgery?
(3) Can this information be harnessed to individualize procedures?

Prospective databases of patients undergoing psychiatric neurosurgery including standardized clinical and neurocognitive evaluations, neuroimaging protocols, and follow-up data are needed to address these questions. Promising routes of exploring each question already exist however.

The ability to predict response to an invasive intervention, especially a permanent one such as a brain lesion, would be extremely useful. Progress towards this goal continues to be made. One potential modality for predicting response is preoperative F-18-fluorodeoxyglucose-positron-emission-tomography (FDG-PET). FDG-PET has been utilized to demonstrate loci of hypermetabolism that may correlate to treatment response in patients undergoing cingulotomy for OCD [82] and MDD [83]. Patient anatomy itself may also provide indices of prediction of response to cingulotomy. In a retrospective assessment of structural imaging of responders and nonresponders to cingulotomy, dACC grey matter volume, as well as laterality differences in connectivity of key CSTC nodes, predicted clinical response [74]. Taken together, these results indicate the potential for using structural and metabolic brain imaging as a means of predicting response to neurosurgical intervention for refractory psychiatric disease.

Neuroimaging approaches can further provide information about how the therapeutic response develops. Therapeutic efficacy in ablative limbic system surgery typically occurs over many months [36•, 66•]. Thus, an important question to address is whether anatomical and functional plasticity changes can be observed longitudinally with modalities like structural MRI, PET, DTI, and resting state fMRI. Plasticity within CSTC circuits may mediate specific symptomatic changes based on lesion location. Tracking changes in neuroimaging would thus allow for better definition of how lesion location affects clinical symptomatology. Moreover, multiple lesion procedures seem to provide benefit in some patients. For example, in some patients who were not responsive to cingulotomy, completion of limbic leucotomy provided therapeutic benefit [12, 66•, 80]. What differences in symptomatology and plasticity are at play in these patients compared to those who respond to an alternative procedure? Further information about response patterns could presumably lead to optimal targets as defined by the specific clinical manifestations of the patient (i.e., patients with certain symptoms respond better to certain procedures).

Indeed, a major goal of psychiatric neurosurgery is targeting on an individualized basis. The diverse symptomatology of psychiatric disorders may reflect differential involvement of CSTC circuits. As a result, a lesion in a specific location may be greatly beneficial for one patient, but marginally so in someone else. Thus, better understanding of dysfunctional circuits is needed in conjunction with how they correspond to symptomatology. In doing so, more specific targets may theoretically be designed that vary based on individual symptom constellations. Accomplishing such individualization of treatment will require parallel progress in defining pathological circuits and improving efficacy of procedures. The involvement of multi-disciplinary teams, with psychiatrists, neurosurgeons, neuropsychologists, neurologists, and cognitive scientists, is therefore essential. Rationally designed targets defined with this level of detail will ideally reduce adverse events as well as provide better outcomes for patients.

Conclusion

In the decades since the initial forays into psychiatric neurosurgery, much progress has been made in understanding the physiology and pathophysiology of the limbic system. Importantly, the limbic subset of the CSTC network has been elucidated in progressively greater detail. Dysfunction in this circuit serves as a common mechanistic link between psychiatric disorders such as obsessive-compulsive disorder, major depressive disorder, and many others. Using progressively more refined neuroimaging tools, structural and functional correlates of CSTC network pathology have been elaborated in order to more precisely define targets. Current ablative limbic system procedures, including dorsal anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy, and limbic leucotomy, thus serve as efficacious therapeutic interventions for those who have exhausted all conventional options. Moreover, the neuroimaging and behavioral data that arise from these procedures are a means of probing pathological circuits to better define disease pathways. With better capability to predict response, better methods of tracking response, and individualized patient targeting, efficacy and safety will improve as distinct patient symptomatology is targeted.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

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