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The History and Future of Ablative Neurosurgery for Major Depressive Disorder

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Treatment-resistant depression · Major depressive disorder · Neurosurgery for mental disease

Abstract
Background: There is an urgent need to develop safe and effective treatments for patients with treatment-resistant depression (TRD). Several neurosurgical procedures have been developed to treat the dysfunctional brain circuits implicated in major depression. ***Objectives:*** This review describes the most common ablative procedures used to treat major depressive disorder: anterior cingulotomy, subcaudate tractotomy, limbic leucotomy, and anterior capsulotomy. The efficacy and safety of each are discussed and compared with other current and emerging modalities, including deep brain stimulation (DBS) and MR-guided focused ultrasound (MRgFUS). ***Methods:*** The PubMed and MEDLINE electronic databases were used in this study, through July 2016. Keywords, including "treatment resistant depression," and "ablative neurosurgery," etc. were used to generate reference hits. ***Results:*** Approximately a third to half of patients who underwent ablative procedures achieved a treatment response and/or remission. The efficacy and safety profiles corresponding to both ablative procedures and DBS were very similar. ***Conclusions:*** The longitudinal experience with ablative procedures shows that there remains an important role for accurate, discrete lesions in disrupting affective circuitry in the treatment of TRD. New modalities, such as MRgFUS, have the potential to further improve the accuracy of ablative procedures, while enhancing safety by obviating the need for open brain surgery.

Introduction

Major depressive disorder (MDD) has been recognized throughout much of human history, with the earliest descriptions in the Hippocratic era ascribing the disease to dysfunction of the melancholic humour [1]. In Canada, the 1-year prevalence of MDD is estimated to be between 3.2 and 4.6% [2]. Furthermore, recent studies estimate the lifetime prevalence of MDD to be between 15 and 20% [3, 4]. Major depression is a highly heterogeneous disorder with symptoms affecting nearly every behavioural domain, including mood, sleep, and sexual and motor functioning. Current diagnostic criteria, accord-

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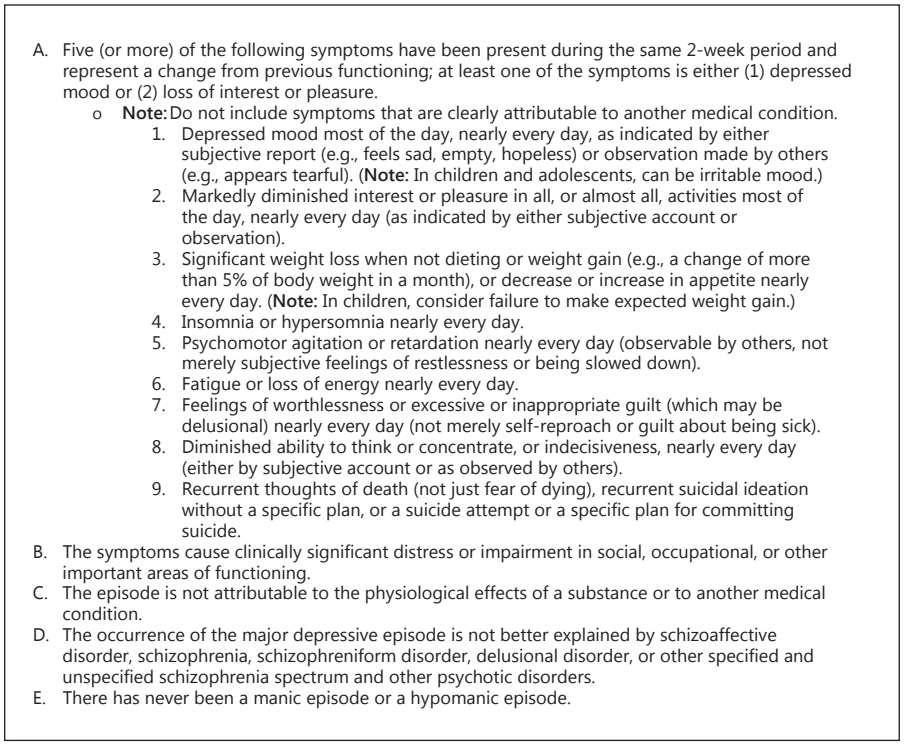

Fig. 1. Diagnostic criteria for MDD according to the fifth edition of the Diagnostic and Statistical Manual (DSM-V) [5].

ing to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [5], include depressive symptoms for a continuous period of at least 2 weeks, and unrelated to other causes, like bereavement or other mood disorders, such as bipolar disease (Fig. 1).

The disease burden of MDD is substantial. Patients often report adverse impacts on personal relationships and employment, and are subject to impaired general functioning [6]. Greenberg et al. [7] estimated the total cost of depression in 2000 in the USA to be nearly USD 82 billion. Total costs include direct expenditures on primary health care utilization, as well as indirect costs such as impacts on employment and disability [7, 8]. In the USA alone, the estimated number of people with MDD increased from 13.8 to 15.4 million adults between 2005 and 2010, with the incidence of MDD expected to increase [9].

The first-line treatment of MDD is pharmacotherapy. Yet the majority of patients will fail to reach remission with a single, adequate course of pharmacotherapy, and are commonly prescribed further forms of conventional treatment, including additional pharmacotherapy, psychotherapy, and electroconvulsive therapy [10, 11]. While the majority of patients diagnosed with MDD will respond to some combination of conventional therapies, up to a third of patients will not reach remission despite optimal care and can be classified as having treatment-resistant depression (TRD) [10, 12]. The disease burden in this patient population is more severe, with suicide rates approaching 15% [12–14]. A recent study suggests that the medical costs are 27.3% greater for patients with TRD compared to patients with chronic MDD, further adding to the economic burden associated with the disease [6].

Due to the serious and life-threatening nature of TRD, and the limitations of conventional treatment approaches, several neurosurgical procedures have been developed that target critical brain circuits involved in aberrant mood. This review traces the history of ablative procedures for major depression while attempting to define the current role for lesional surgery. There is a long history of stereotactic surgery for psychiatric disease, and indeed some of the first indications for ablative procedures were refractory mental illness [15]. Early procedures, such as the standard leucotomy, lacked precision and were applied with little to no regulatory oversight, casting a shadow over the field [16–18]. While some patients reportedly benefited from the wholesale destruction of frontal white matter tracts, many sustained permanent changes to their personality [16–18]. Current efforts to treat mental illness with neurosurgery and to investigate novel approaches in clinical trials must adhere strictly to ethical

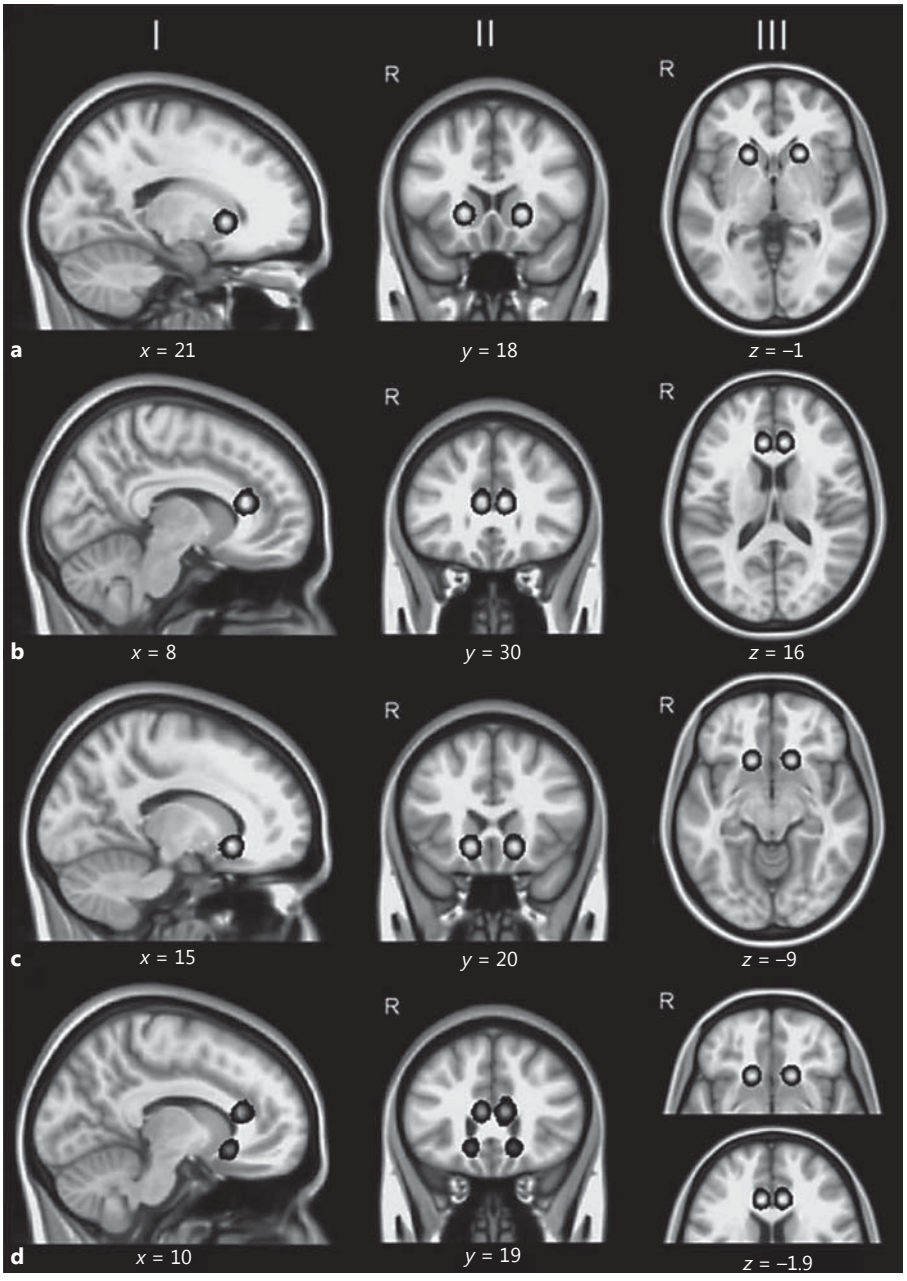

Fig. 2. Theoretical lesion sites corresponding to bilateral ablative surgeries for the treatment of TRD: anterior capsulotomy (**a**), anterior cingulotomy (**b**), SST (**c**), and limbic leucotomy (**d**). The left (I), centre (II), and right columns (III) correspond to T1-weighted sagittal, coronal, and axial views, respectively [74]. Reprinted with permission from Macmillan Publishers Ltd. [74], copyright 2010.

guidelines, prescribed both by the academic community as well as local and federal regulatory bodies. Although a detailed discussion of the ethical challenges facing research in psychiatric surgery is outside the scope of this paper, several recent guidelines have been published [19, 20].

The need to develop safe and effective treatments for psychiatric disorders has further spurred technological advances in the field, including the development of gamma knife radiosurgery [21]. Interest in lesional treatments for MDD is now increasing because of recent advances in neuroimaging, and the development of non-invasive surgical approaches, such as MR-guided focused ultrasound (MRgFUS) [22]. As such, this review describes the most common ablative procedures that have been used to treat MDD: anterior cingulotomy, subcaudate tractotomy, limbic leucotomy, and anterior capsulotomy (Fig. 2). The safety and efficacy of each procedure is discussed. Where available, efficacy was assessed based on standardized depression rating scales, including the clinician-rated Ham-

Table 1. Ablative procedure outcomes for studies with standardized assessment

Study	Procedure	Number/type of patients	Outcome at most recent follow-up
Ballantine et al. [29], 1987	anterior cingulotomy	118 (83 with unipolar affective disorder)	77 patients (65.3%) were at least "considerably" improved, 25 patients (21.2%) were either unchanged or showed slight improvement, 16 patients (13.6%) were worse; 14 patients (11.9%) had committed suicide
Shields et al. [30], 2008	anterior cingulotomy	33 total patients (17 with MDD)	response defined as 50% reduction in the Beck Depression Inventory (BDI) and Clinical Global Improvement (CGI) of 2 or less; partial response defined as 35% reduction in BDI and CGI of 2 or less; of 33 patients, 7 patients (21.2%) were responders, 6 (18.2%) were partial responders, and 20 (60.6%) did not respond
Steele et al. [31], 2008	anterior cingulotomy	8 MDD patients	response defined as ≥50% reduction in HAMD-17 and MADRS; remission defined as HAMD-17 ≤7 and MADRS ≤10; of 8 patients, 5 (62.5%) were responders, with 3 (37.5%) in remission; 2 (25%) were non-responders, and 1 (12.5%) deteriorated
Hodgkiss et al. [34], 1995	stereotactic subcaudate tractotomy	286 patients (183 with MDD)	clinical outcome based on physician assessment; 63 patients (34.4%) were "well" or "recovered," 58 (31.7%) were "improved," 57 (31.1%) were "unchanged" or "worse," and 5 (2.7%) died for reasons unrelated to the neurosurgical procedure; no suicides were reported in the first postoperative year
Kim et al. [36], 2002	stereotactic subcaudate tractotomy	7 MDD patients	at the most recent follow-up, 5 patients (71.4%) were classified as responders, while 2 patients (28.6%) did not respond; average HAMD-17 scores for the group decreased from 39.7 (SD 3.3) pre-operatively to 15.7 (SD 6.1) at the last follow-up; the only AE reported was transient urinary incontinence in 1 patient
Montoya et al. [41], 2002	limbic leucotomy	21 total patients (6 with MDD)	1 patient committed suicide after the procedure; postoperative BDI scores were collected for the other 5 patients with MDD, and 2 patients (40%) were identified as responders
Christmas et al. [42], 2011	anterior capsulotomy	20 patients with MDD	response defined as ≥50% reduction in HAMD-17 and MADRS; remission defined as HAMD-17 ≤7 and MADRS ≤10; of 20 patients, 10 (50%) were classified as responders, and 8 (40%) were remitters
Riestra et al. [43], 2011	anterior capsulotomy	1 patient with MDD and OCD	at last follow-up (3 years), the HAMD-17 score had reduced from 35 to 16 (54.3% reduction); the Y-BOCS score also decreased from 26 to 1 (96.2% decrease)
Hurwitz et al. [44], 2012	anterior capsulotomy	8 MDD patients	at the 18-month follow-up, 3 patients (37.5%) were responders, with 2 (25%) in remission; 3 patients (37.5%) were partial responders, and 1 patient (12.5%) did not respond; 1 patient (12.5%) presented with a complicated postoperative course and died

ilton Rating Scale for Depression (HAMD-17), the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS), and the self-rated Beck Depression Inventory (BDI). While there are differences between these, all are frequently used to assess the severity of depressive symptoms in clinical populations, as well as improvements in symptoms over time [23–25]. To generate references, the PubMed and MEDLINE databases were used, through July 2016. Key words, including "treatment resistant depression," "psychosurgery," and "ablative surgery" were used in combination without language restrictions. All relevant studies are discussed, and those studies that prospectively rated clinical outcomes are summarized in Table 1. Studies that utilized a clinician-rated scale frequently varied in their definition of treatment response. However, unless otherwise stated in our discussion, treatment response is defined as a ≥50% reduction in HAMD-17 or MADRS, while remission is defined as HAMD-17 ≤7 or MADRS ≤10, in accordance with the generally accepted criteria in the depression literature. We go on to compare the results of ablative procedures with those of deep brain stimulation (DBS) both in terms of safety and efficacy. Finally, we consider the future of ablative procedures for the treatment of MDD in the context of developing surgical technologies.

Anterior Cingulotomy

The history of cingulotomy for psychiatric disease spans several decades, to the earliest days of neurosurgery. Much of this work predated the development of valid outcome measures in depression, and early reports consisted of narrative descriptions of patient outcomes and complications, with patients typically classified as improved or not. The earliest reported anterior cingulotomy series was by Whitty et al. [26], who treated patients with schizophrenia in addition to several cases of "melancholia." The procedure involved the bilateral removal of a block of tissue from the Brodmann area 24 with a volume of 40 × 10 × 10 mm [26]. The authors reported modest improvements for patients with depression [26]. Foltz and White [27] used anterior cingulotomy to treat intractable pain in 16 patients, with their pro-

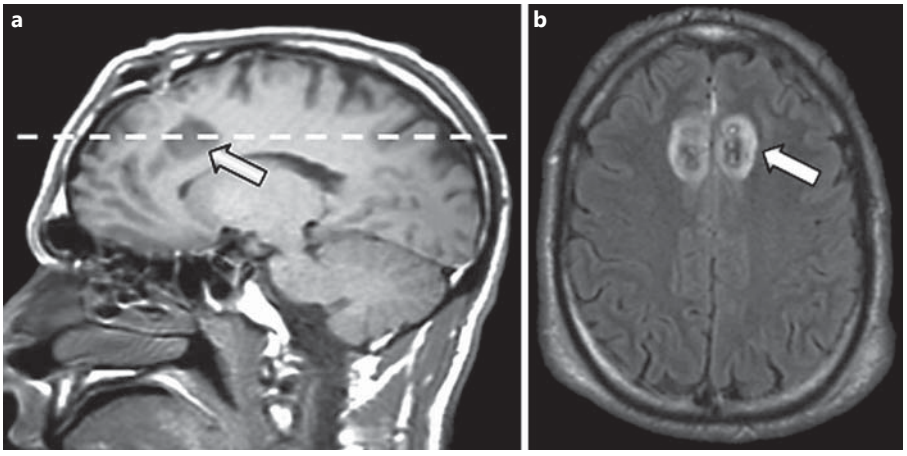

Fig. 3. Representative postoperative MRI images following bilateral anterior cingulotomy. A T1-weighted sagittal image (**a**) and T2-weighted axial image (**b**) are shown, with white arrows indicating the lesion position. Reprinted from Shields et al. [30], copyright 2008, with permission from Elsevier.

cedure requiring several bilateral lesions in the cingulum bundle. In several cases, unilateral lesions were performed, with the authors noting that these patients did not benefit as much as patients undergoing bilateral treatment [27]. Overall, the authors reported that 14 out of 16 (87%) patients benefited from the procedure.

Ballantine et al. [28] improved on the cingulotomy procedure by utilizing plain X-rays and a centimetre scale which was fixed to the patient's scalp. The cingulate bundle was localized by air ventriculography, 10 mm above the lateral ventricles, 6.6 mm lateral from the midline, and 25 mm posterior to the anterior horns of the lateral ventricles. Lesions were created by thermistor electrodes, which were inserted bilaterally and heated to 80–85°C for 100 s. The lesions produced were found to be 10 × 20 mm in size, in the sagittal plane [28]. Postoperative data gathered from 40 patients showed that 36 (90%) were improved to some degree, with 8 of those (20%) classified as completely recovered [28]. In a later study, Ballantine et al. [29] reported the combined results for 120 patients with affective disorders and major depression, with 83 of these diagnosed with unipolar affective disorder. Postoperative results were available for 118 patients. Of these, 77 (65.3%) were at least "considerably" improved, while 25 (21.2 %) were either unchanged or showed slight improvement, and 2 patients (1.7%) were worse [29]. Fourteen patients (11.9%) had died by suicide at the most recent follow-up. There were no deaths, but postoperative seizures occurred in 1% of patients [29]. Two patients were left hemiplegic as a result of intracerebral haemorrhage following the operation [29]. The authors reported that, in their experience with 696 bilateral cingulotomy procedures, patients did not suffer adverse effects related to intellectual function, emotional tone, or social control [29].

More recently, Shields et al. [30] evaluated the effects of anterior cingulotomy on 33 patients with TRD at Massachusetts General Hospital. Each patient first underwent a bilateral anterior cingulotomy with single lesions [30]. Additional lesions were created (up to 3 lesions bilaterally) if the patient failed to respond to this first procedure [30]. However, the authors noted that many of the early patients failed to respond to single bilateral lesions, and as a result, refined their initial cingulotomy surgery to include 3 bilateral lesion targets. The first target was located 20–25 mm posterior to the anterior horn of the lateral ventricle, 7 mm lateral to the midline, and 5 mm above the corpus callosum [30]. The second and third lesions were placed 7 mm anterior and 2 mm inferior, and 14 mm anterior and 4 mm inferior with respect to the first lesion to conform to the shape of the anterior cingulate gyrus (Fig. 3) [30]. Postsurgical analysis revealed that the average total volume of the 3 lesions was 3.58 cm^3 (SD 1.2, range 1.97–5.83) [30]. Of the 33 patients who underwent the procedure, 7 (21.2%) were responders, 6 (18.2%) were partial responders, and 20 (60.6%) did not respond [30]. Patients still classified as non-responders after 12 months were offered an additional procedure, either a repeat anterior cingulotomy, or a bilateral subcaudate tractotomy (constituting a full limbic leucotomy) [30]. Seven of the 20 non-responders in this patient series went on to receive a subcaudate tractotomy, the results of which are reviewed below [30]. The authors reported the adverse event (AE) profile for the 33 patients who underwent the anterior cingulotomy procedure [30]. Transient AEs, which resolved in days to several months, included uri-

nary incontinence (4 patients, 12.1%), periodic limb movements (1 patient, 3.0%), and difficulty with the pronunciation of some words (1 patient, 3%) [30]. AEs that persisted at the most recent follow-up included subjective memory loss (1 patient, 3%) and intracranial abscess (1 patient, 3%), which resolved after 2 months of antibiotic administration [30]. One patient (3%) also experienced tonic-clonic seizures, which were controlled with phenytoin [30].

Steele et al. [31] performed anterior cingulotomy on 8 patients with TRD at Royal Cornhill Hospital. Bilateral lesions were placed 20 mm posterior to the tip of the anterior horn of the lateral ventricles, 7 mm lateral to the midline, and 1 mm superior to the roof of the lateral ventricles [31]. The postoperative results were encouraging. Twelve months postoperatively, 5 patients (62.5%) were responders (with 3 of these patients meeting the a priori criteria for remission). Two patients (25%) were non-responders, and 1 patient (12.5%) deteriorated [31]. Postoperative MR imaging analysis revealed variation in lesion placement in the anteroposterior (*y*-co-ordinate) axis. The authors reported that more anterior-placed lesions were predictive of a greater clinical response, as indicated by larger decreases in both the HAMD-17 as well as the MADRS scores [31]. Furthermore, smaller total lesion volumes were significantly correlated with a better clinical response, as indicated by greater reductions in the HAMD-17 and MADRS scores [31]. Best fit linear regression lines indicate that total lesion volumes between 1,000 and 2,000 mm^3 were associated with an optimal clinical response [31].

Subcaudate Tractotomy

The refined orbital undercut was a procedure introduced by Knight [32], and involves the destruction of 3 different white matter tracts: (1) projection fibres descending from both the frontal cortex and area 13 to the ventromedial nucleus of the hypothalamus, (2) amygdala white matter, and (3) connections between area 13 and the frontal cortex. Of 221 patients with intractable depression who underwent the procedure, 155 (70.1%) were deemed not to require further medical care, reporting either with slight residual symptoms or no symptoms [32]. These results should be interpreted with caution, however, given the absence of objective depression rating scales and the assessment of serious AEs, such as personality change [32].

Knight [32, 33] observed that positive clinical outcomes seemed to correlate with the posterior extent of the lesion. The procedure was therefore modified to include only the posterior 20-mm portion of the original lesion, which was thought to reduce unnecessary brain scarring causing seizures and unwanted personality changes [33]. Anatomically, this area consisted of the substantia innominata immediately inferior and slightly anterior to the head of the caudate [33]. The modified procedure involved the bilateral stereotactic placement of 2 rows of 4 radioactive yttrium (^{90}Y) seeds which caused bilateral lesions 20 × 20 × 5 mm in size [33]. Of the 23 patients who received the operation for depression, 20 (87.0%) reported either slight depressive symptoms (with no treatment required) or no depressive symptoms at the most recent follow-up [33].

In 1995, Hodgkiss et al. [34] from the Geoffrey Knight National Unit for Affective Disorders reported results from a cohort of 183 patients who underwent stereotactic subcaudate tractotomy (SST) for depression. In the first 12 months postsurgery there were no reported deaths due to suicide [34]. In all, 63 patients (34.4%) were characterized as well or recovered, 58 (31.7%) were improved, 57 (31.1%) were unchanged or worse, and 5 (2.7%) had died for reasons unrelated to the neurosurgical procedure [34].

The production of radioactive yttrium beads was discontinued in 1998, and Knight's SST required a different ablative modality [33, 35]. Radiofrequency thermistor electrodes were employed, and heated to 80°C for 40 s to produce 10 bilateral lesions, created in 2 rows of 5, which were separated by a distance of 10 mm [35]. Researchers reported that total lesion volumes created using radiofrequency electrodes were comparable to those created using yttrium beads. They also noted that this new technique seemed to reduce adverse side effects associated with the procedure [35].

More recently, Kim et al. [36] performed subcaudate tractotomy in 7 patients with medically intractable depression. The procedure was performed by creating single bilateral lesions 12 mm anterior to the tuberculum sellae, 10–15 mm superior to the floor of the anterior fossa, and 6–14 mm from the midline [36]. The authors did not report the volume of the lesions generated. At the most recent follow-up, which was a minimum of 12 months after the operation, 5 patients (71.4%) were classified as responders (>50% reduction in HAMD-17 score from baseline), and 2 were improved but failed to reach a 50% HAMD-17 reduction [36]. There were no persistent or serious AEs reported.

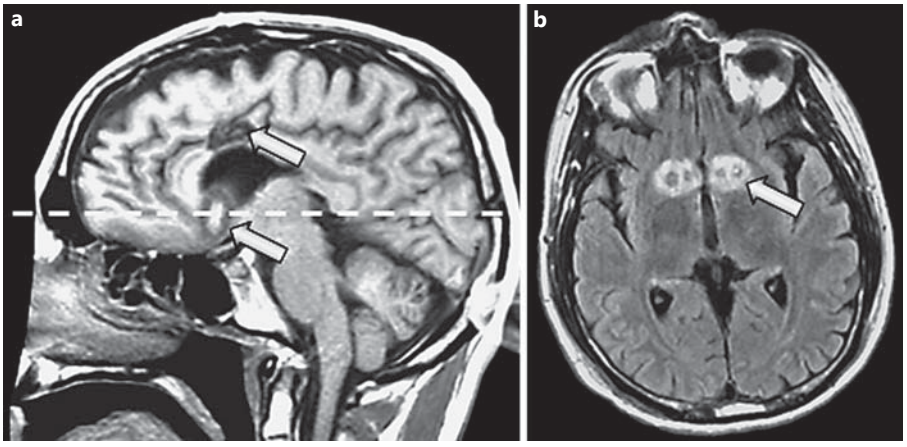

Fig. 4. Representative postoperative MRI images following bilateral limbic leucotomy. T1-weighted sagittal (**a**) and T2-weighted axial (**b**) images are shown, with arrows indicating lesion locations. Note that the level of the axial image corresponds to the subcaudate tractotomy component of the limbic leucotomy. Reprinted from Shields et al. [30], copyright 2008, with permission from Elsevier.

Limbic Leucotomy

Kelly and colleagues [37–40] performed a limbic leucotomy on 9 patients with MDD. The streamlined procedure involved 3 lesions placed bilaterally in the lower medial quadrant of the frontal lobe, consistent with the medial portion of Knight's procedure for SST [37–40]. In addition, 2 lesions were placed bilaterally in the anterior cingulate gyrus, although variations of lesion placement were carried out in some early cases, prior to procedural refinement [37–40]. Cryogenic lesions, approximately 8 mm in diameter, were created by cooling an exposed probe tip to –70°C for 5 min [37–40]. Researchers reported that patients with MDD who underwent limbic leucotomy did not present with emotional blunting, postoperative epilepsy, or excessive weight gain, nor did they exhibit postoperative changes in intelligence measures [37–40]. At the 6-week follow-up, the authors reported that 3 patients (33.3%) were "symptom-free," 3 patients (33.3%) were "much improved," and 3 (33.3%) were "improved" [40]. At the 16-month follow-up, 7 of 9 patients (77.8%) were found to still be improved to some degree, while 2 patients (22.2%) were now classified as "unchanged" [40]. While average HAMD-17 and BDI scale scores were published across all patients, the authors did not delineate scores based on diagnostic grouping, making these results more difficult to interpret [40]. To date, this group has carried out the limbic leucotomy on 100 patients with a variety of affective disorders [40]. In 100 procedures, only 1 serious side effect was reported, namely a transient postoperative memory deficit [40]. The authors attributed the memory impairment to a lesion placed more posteriorly than originally planned [40]. More commonly reported AEs with limbic leucotomy include headache, severe "laziness," stereotyped perseverative behaviour, and inadequate sphincter control [40].

Montoya et al. [41] of Massachusetts General Hospital reported 21 psychiatric patients who underwent bilateral limbic leucotomy, 6 of whom had MDD [41]. Based on clinician ratings postsurgery, 3 patients (50%) with MDD were classified as responders. One patient with MDD committed suicide postsurgery [41]. Of the 21 total patients who underwent limbic leucotomy, 5 (23.7%) had transient urinary incontinence, 5 (23.7%) complained of short-term memory problems, of which 2 continued to have memory problems at the most recent follow-up [41]. Four patients (19%) experienced seizures postoperatively. Three of the 4 patients suffered only a single event, with 1 patient developing epilepsy following surgery [41]. Other side effects included agitation, fever, apathy, and somnolence, all of which were transient [41].

As discussed above, Shields et al. [30] performed anterior cingulotomy on 33 patients with major depression. Twenty patients did not respond adequately to the cingulotomy procedure, and 16 of these patients went on to receive an additional procedure, either repeat anterior cingulotomy, or bilateral subcaudate tractotomy. Of the 16 patients, 7 underwent SST, culminating in a full limbic leucotomy (Fig. 4) [30]. Although the reported results were not categorized by which additional procedure was carried out, the authors reported that at least partial benefit was garnered by 12 (75%) of these patients, with 4 (25%) classified as responders [30].

Anterior Capsulotomy

Anterior capsulotomy has only recently been utilized to treat TRD. Christmas et al. [42] performed the procedure on 20 patients with MDD and at the mean follow-up of 7.0 years (SD 3.4 years), 10 patients (50%) were treatment responders, while 8 of those (40%) met the a priori definition of remission. Overall, 11 patients (55%) were improved, 7 (35%) were unchanged, and 2 (10%) had deteriorated [42]. AEs immediately after the procedure included urinary incontinence in 3 patients (15%), headache in 8 (40%), confusion in 5 (25%), and tiredness in 3 (15%) [42]. Sustained AEs included headache in 3 patients (15%) and urinary incontinence in 2 patients (10%) [42]. There were no recorded deaths by suicide [42].

Riestra et al. [43] completed a unilateral anterior capsulotomy on a single patient with MDD and secondary obsessive-compulsive disorder (OCD). The rationale for a unilateral procedure was an FDG-PET (fluorodeoxyglucose positron emission tomography) scan done prior to surgery, showing metabolic activity of several limbic structures suggestive of unilateral MDD pathology [43]. The surgery was well tolerated, and the patient achieved a 57% reduction in HAMD-17 score at evaluation after 1 and 2 years, and a 54% reduction at year 3 [43]. The patient's Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score also decreased 58, 77, and 96% at each of the annual check-ups [43]. While this case is intriguing, it is as yet unclear whether an increased clinical benefit from unilateral ablative procedures can be reliably predicted.

Hurwitz et al. [44] of the Vancouver Limbic Surgery Group (VLSG) reported 8 patients with MDD who underwent bilateral anterior capsulotomy using radiofrequency lesions. MR imaging conducted postoperatively found the ellipsoidal lesion volumes to be, on average, $4.8 \times 4.4 \times 14.2$ mm, and $5.8 \times 5.1 \times 14.8$ mm in diameter for the left and right hemispheres, respectively [44]. The procedure was well-tolerated by 7 of the 8 patients, with 1 patient developing akinetic mutism followed by dementia with parkinsonism, ultimately dying 2 years postoperatively due to renal failure [44]. Autopsy revealed extensive arteriolosclerosis secondary to a 40-year history of hypertension, which was deemed responsible for his vascular dementia [44]. Overall, 4 out of 8 patients (50%) were classified as responders (greater than 50% reduction in pre-operative BDI score) between 24 and 36 months postoperatively [44]. Transient AEs included postoperative confusion (2 patients, 25.0%), fatigue (2 patients, 25.0%), subjective emotional blunting (2 patients, 25.0%), and difficulty formulating higher-order thoughts and ideas (1 patient, 12.5%) [44]. Several patients suffered a decline in neuropsychological capacities, including visuoconstruction (1 patient, 12.5%) and semantic memory (2 patients, 25%) [44]. One patient (12.5%) suffered a decline in several neuropsychological measures, including attention, mental speed, recent verbal memory, and problem solving [44]. Hurwitz et al. [44] used a battery of neuropsychological tests at predetermined intervals postoperatively to detect AEs. Their rigorous and conservative definitions of AEs may explain the relatively greater prevalence of AEs in this patient series. Despite the AE profile listed here, the authors reported that the vast majority of neuropsychological domains were either unchanged or improved [44].

Non-Invasive Ablative Surgery

Current lesional surgery involves the application of a stereotactic head frame, MRI-guided targeting, a cranial window, and transcortical passage of an electrode, the tip of which is heated to achieve a thermocoagulative lesion. Although rare, surgical complications, such as intraparenchymal haemorrhage and infection, can occur, and must be balanced against the possibility of clinical benefit. By contrast, other surgical modalities, such as gamma knife radiation surgery (GKRS) and MRgFUS, now have the potential to enhance the safety of ablative procedures by obviating the need for an open operation and brain penetration.

Gamma Knife Radiation Surgery

GKRS utilizes ionizing radiation which, when focused to a specific point in the brain, provides a radiation dose sufficient to cause neuronal cell death [45]. The advantage of GKRS is its non-invasive nature, and the ability to treat patients not eligible for, or who cannot tolerate, an open neurosurgical procedure. Disadvantages include the use of radiation, the latency to the clinical and radiographic effect, and the limitations of repeat treatments [22]. Radiation exposure is additive, and multiple procedures with exposure to ionizing radiation increases the risk of unwanted side effects to adjacent tissue [46]. Although GKRS is currently used for a wide range of clinical indications, including vascular malformations, brain tumours, and movement disorders [45], it has not to date been used to treat TRD. Several open-label GKRS anterior capsulotomy trials have been conducted, however, to treat refractory OCD. Ruck et al. [47] reported 9 refractory OCD patients who underwent bilateral GKRS capsu-

lotomy, with either 1 or 3 isocentres bilaterally. The average preoperative Y-BOCS score was 33.4 (SD 4.2) and HAMD-17 score was 20.1 (SD 5.8), and at 1 year the Y-BOCS was reduced to 17 (SD 13.9) while the HAMD-17 score had reduced to 12.4 (SD 8.5). At the most recent follow-up, 5 patients (55.5%) were classified as remitters (Y-BOCS score ≤15) [47]. The adverse effects of surgery included problems with executive functioning, disinhibition, apathy, and weight gain [47]. The authors noted that smaller lesion volumes were correlated with fewer adverse side effects, and also with a greater reduction on the Y-BOCS scale [47]. While depression was not the primary diagnosis for these patients, it is notable that GKRS capsulotomy was associated with significant reductions in HAMD-17 scores [47].

Lopes et al. [48] recently reported the first randomized, double-blind, sham-controlled study using GKRS for any psychiatric disorder, investigating capsulotomy in 16 patients with refractory OCD. Such studies are critical to establishing the feasibility of randomized trials in lesional surgery in psychiatry, and given the similarity of the target in question, can inform depression treatments and trials. The 16 patients were randomly assigned to either an active treatment or control, sham treatment arm. Patients in the treatment group received 2 bilateral lesions, with the isocentres targeted to the ventral border of the internal capsule, in the regions of the ventral capsule/ventral striatum [48]. At the 12-month follow-up, 2 patients (25%) were classified as responders (≥35% reduction in Y-BOCS score), and at the last follow-up (54 months), 5 patients (62.5%) were responders [48]. None of the patients receiving sham surgery were classified as responders at either time point [48]. After unblinding, patients in the sham-treatment group were offered the GKRS procedure [48]. Four elected to receive the procedure, and at the 12-month follow-up, 2 of them (50%) were responders [48]. In total, 7 out of 12 patients (58.3%) were responders to radiosurgery [48]. The majority of the adverse effects were transient and included nausea, weight gain, headache, and mania/hypomania [48]. The most serious AEs occurred in a patient who presented with perilesional oedema concomitant with visual hallucinations and delirium, as well as impaired executive function and memory. These symptoms persisted for 5 months [48]. At the last follow-up, this patient was not a responder and had developed a 6-mm asymptomatic brain cyst.

Magnetic Resonance-Guided Focused Ultrasound

MRgFUS produces an intracranial lesion at the convergence point of multiple sources of acoustic energy within a specially designed helmet, under real-time MRI guidance [46]. By utilizing multisource ultrasound, discrete lesions can be created following a sufficient increase in temperature in the target tissue, causing cell death by necrosis and/or apoptosis [22, 49]. Recent advances in focused ultrasound (FUS) technology have made it possible to generate lesions in the brain through the intact skull [22, 49]. Similar to GKRS, MRgFUS is a non-invasive procedure, not requiring a skin incision, burr hole, or transcortical passage, hence reducing the theoretical risk of intracranial complications [22, 49, 50]. MRI guidance is employed throughout the procedure to visualize the production of the lesion, and to assist with the correct targeting and shaping of the lesion [22]. Another advantage of MRgFUS is that the surgical team can apply high-frequency ultrasound at sublesional temperatures to reversibly modulate the activity of the target tissue and examine the patient for clinical effects, including potential AEs, before proceeding to apply lesion-generating temperatures [46]. In this way, surgeons can visualize the position of the lesion site using MR thermometry without irreversibly affecting the tissue [22, 46]. The lesion volumes created with FUS have been found to be relatively stable [51, 52]. Furthermore, since the lesion is created by mechanical forces, multiple FUS procedures can be carried out to tailor the volume of the lesion with a decreased risk of adverse additive effects inherent with GKRS [46]. The advantages of MRgFUS as a lesion modality provided the impetus for its use in the treatment of various indications, including intractable pain and essential tremor [51, 53–55].

Since the ability to precisely place small-volume lesions has been associated with an increased clinical response for patients receiving anterior cingulotomy for TRD as well as anterior capsulotomy for OCD, MRgFUS may be an especially effective lesion modality in the treatment of psychiatric disease [31, 47]. Jung et al. [52] recently conducted a proof-of-concept study using MRgFUS to perform anterior capsulotomy in 4 patients with refractory OCD. The average Y-BOCS score prior to surgery was 35.3 (SD 1.9), and at last follow-up (6 months) the average score was reduced to 23.5 (SD 4.9), with 2 patients (50%) classified as responders (≥35% reduction in the Y-BOCS score) [52]. The patients' depression and anxiety symptoms were also significantly reduced after the procedure. The average HAM-D score was 22.5 (SD 4.2) pre-operatively, which was reduced to 8.8 (SD 3.3) at the 6-month follow-up [52]. The authors reported no serious or permanent AEs in these patients. Common complications with ablative procedures, including confusion,

apathy, as well as impaired executive functioning, were not observed [52]. However, during the procedure all patients felt transient headaches, and nausea/dizziness was observed in 3 patients (75%) [52].

Combined Stimulation and Ablation Procedures

A recent study investigated whether employing both DBS and an ablative procedure for 2 different targets implicated in MDD would result in additional clinical benefits [56]. Chang et al. [56] performed bilateral anterior cingulotomy in addition to ventral capsule/ventral striatum (VC/VS) DBS on 3 patients with OCD and concomitant TRD. Both targets have been shown to be effective ablative and DBS targets in the treatment of MDD [57]. At the 36-month follow-up, all 3 patients exhibited a greater than 35% improvement in Y-BOCS scores, and greater than 36% improvement in HDRS scores [56]. While patients showed significant responses to this dual procedure, such results cannot be used to conclude that the use of combined ablative and DBS procedures leads to an additive clinical response in patients with OCD and MDD [56]. In another study, Neimat et al. [58] reported results from a patient who underwent multiple surgical interventions to treat her MDD. The patient first received bilateral cingulotomy, which provided some benefit weeks after the procedure but failed to provide a sustained clinical response. The patient then underwent subcallosal cingulate cortex (SCC) DBS with a subsequent reduction in HAMD-17 score from 19 prior to surgery, to 11, 8, and 7 at 3, 6, and 12 months of follow-up, respectively [58]. Whether improved depressive symptoms are due to SCC DBS alone, or whether the combined cingulotomy played a role in the observed reduction in depressive symptoms, cannot be determined from this single case.

Stimulation or Ablation? The Role of Lesions in Depression

With the development and rapid adoption of DBS in the field of functional neurosurgery, the question remains of what, if any, is the role for ablative procedures. This is a question not unique to TRD. Unfortunately, there currently exists limited clinical evidence to compare and select between DBS and lesions for depression; however, several important points can be raised regarding both modalities to help tailor treatments to specific clinical scenarios.

The clinical effects of stimulation and ablation are similar, with at least a third to half of patients, in prospective, open-label studies, achieving a treatment response and/or remission. While multiple targets have been used for TRD, the most common DBS target to date is the SCC. Mayberg et al. [59] first reported 6 patients (5 MDD, 1 bipolar II) who underwent SCC DBS and at the 6-month follow-up 4 (66.7%) patients were responders, and 2 of these responders were also in remission. The only AE was skin infection in 3 (50%) patients [59]. Kennedy et al. [60] reported the long-term follow-up (mean 3.5 years) of 20 SCC DBS patients and found that the previously observed improvements in depressive symptoms were sustained, with 64.3% of patients classified as responders, and 42.9% classified as remitters. Puigdemont et al. [61] reported similar results in a series of 8 patients, wherein at 1 year after the operation, 62.5% of patients were responders and 50% were in remission. The results of open label studies of SCC DBS led to the design of a large, sham-controlled, randomized trial of DBS for refractory depression, the BROADEN study. Interim results from this trial suggested no significant difference between active and sham stimulation, a result similar to that observed at the VC/VS target [62]. Although these results have not yet been published, there is the suggestion that variations in patient selection, illness heterogeneity, and lead placement across surgical centres may have played a role in the results.

The advantage of DBS is the ability to titrate stimulation to clinical effect and control the side effects of overstimulation [57]. It remains unclear, however, in the context of TRD, what the optimal stimulation parameters are, and whether serial adjustments can be linked to enhancing clinical benefit over time. Not enough data and long-term follow-up exists. There are also currently at least 5 other anatomic targets under investigation with DBS for TRD, including the nucleus accumbens [63–67], ventral capsule/ventral striatum [68, 69], inferior thalamic peduncle [70], habenula/lateral habenula [71, 72], and the medial forebrain bundle [73]. Although these do in large part all represent components of the affective regulatory circuit, and in almost all cases are polysynaptically linked, it is unclear which target, if any, is the most effective. Indeed, it may be that the selection of a target may depend on the specific clinical context, such as the presence of specific illness biomarkers or clinical features, such as anhedonia.

Ablative surgery obviates many of the risks and expense associated with a life-long implant. Furthermore, these procedures are also more widely available, and can

be performed efficiently and with limited health care resources. The clinical benefits have been borne out by over half a century of experience, although much of this work has been retrospective, uncontrolled, and involving highly variable patient populations. Nevertheless, the evidence for subcaudate tractotomy, capsulotomy, and particularly cingulotomy, in TRD has been compelling and it appears that a substantial proportion of patients, irrespective of their eligibility for DBS, may benefit from these procedures. The development of non-invasive ablative procedures, especially of MRgFUS, may represent a balance between risk and clinical benefit in highly selected TRD patients.

There are, however, important drawbacks to ablative procedures. Foremost is the fact that lesions, and any potential negative therapeutic outcomes, are permanent. The use of MRgFUS may be advantageous over GKRS in this regard, as it affords the ability to apply low-intensity FUS to reversibly modulate the activity of the target tissue, before proceeding to apply high-intensity FUS to cause an irreversible lesion [46]. There is also a limited ability to tailor structural lesions, as is possible with stimulation. Furthermore, despite several decades of experience with ablative procedures for TRD, studies to date generally report that approximately 30–60% of patients benefited from these procedures (Table 1). Therefore, the majority of TRD patients undergoing ablative surgery do not achieve an optimal clinical response. More experience with a greater number of patients may help to shed light on markers for patients who respond to treatment, which may help improve screening criteria and optimize patient selection. In addition, advances in imaging combined with less invasive lesion techniques (including MRgFUS and GKRS) may help to increase the number of TRD patients that benefit from ablative procedures, and limit postoperative complications.

The safety profiles of ablation and stimulation are distinct, although there are similarities. Both procedures, unless using GKRS or MRgFUS, require a cranial window and transcortical transgression. DBS may be further complicated by device malfunction, breakage, disconnection, and infection. In general, however, the reported AE profile for lesions and stimulation for psychiatric disease have been largely similar. Both procedures were associated with transient perioperative AEs, such as headache, confusion, and incontinence. Serious AEs, like postoperative seizures, cognitive impairment, and suicide, although rare, were also reported after both ablative and stimulation procedures. An inherent advantage of DBS may be the ability to titrate electrical stimulation to potentially reduce or eliminate some of these AEs.

Several factors limit the interpretation of the ablative literature to date, and in particular early reports of lesional procedures. These include rudimentary, or non-existent, neuroimaging to determine optimal targeting preoperatively and confirmation of lesion placement postoperatively, as well as the absence of standardized outcome measures that provide objective assessments of efficacy and comparison between studies. Furthermore, subtler AEs, such as those related to neuropsychologic and cognitive outcomes, were rarely measured. These studies do, however, provide critical information regarding the feasibility of ablative procedures, and are highly suggestive of effectiveness in a proportion of refractory patients that may even exceed the proportion that respond to accepted antidepressant medications. Current advances, including high-resolution neuroimaging, standard outcome measures, sensitive pre- and postoperative neuropsychologic testing, and the coupling of non-invasive treatments with real-time imaging, will build on the historical literature and provide the optimal ingredients for rigorously evaluating the role of lesions in depression.

Conclusion

The results of ablative procedures for TRD have been encouraging, both in terms of effectiveness and safety. While irreversibility is an inherent limitation of lesions, the large experience with stereotactic cingulotomy, subcaudate tractotomy, and capsulotomy has shown that there remains an important role for accurate, discrete lesions in disrupting affective circuitry in the treatment refractory patients. New modalities, such as MRgFUS, have the potential to further improve the accuracy of ablative procedures, while enhancing safety by obviating the need for brain penetration. Clinical trials in TRD comparing lesions with DBS, as well as trials of MRgFUS, will help determine what role, if any, lesions will continue to play in the management of this challenging condition.

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