Critical Review of Palliative Surgical Techniques for Intractable Epilepsy

Susanne Fauser and Josef Zentner

Contents

Abstract Approximately one third of epilepsy patients are not adequately treatable by antiepileptic medication. Curative resective epilepsy surgery can be performed in only a subgroup of these pharmacoresistent patients in whom the epileptogenic focus is localizable and does not overlap with eloquent brain areas. To the remaining patients (with bilateral or multiple epileptogenic foci, with epilepsy onset in eloquent areas, or with no identifiable epileptogenic focus) palliative epilepsy surgery can be offered if they suffer from disabling seizures. Standard palliative procedures currently comprise corpus callosotomy, multiple subpial transections, and vagus nerve stimulation. New approaches such as focus distant deep brain stimulation or direct stimulation of the hippocampus have gained the most interest. Feasibility studies, small pilot studies, and, recently, larger multicenter trials showed

S. Fauser (✉)
Department of Neurosurgery, Epilepsy Center, University of Freiburg,
Breisacher Str. 64, 79106 Freiburg, Germany
e-mail: susanne.fauser@uniklinik-freiburg.de

J. Zentner
Department of Neurosurgery, University of Freiburg,
Freiburg, Germany

N. Akalan, C. Di Rocco (eds.), *Pediatric Epilepsy Surgery*,
Advances and Technical Standards in Neurosurgery,
DOI 10.1007/978-3-7091-1360-8_7, © Springer-Verlag Wien 2012

that direct brain stimulation shall be considered a potential helpful procedure in the field of palliative surgery. Moreover, with the increasing use of stereo-EEG in invasive video-EEG monitoring, stereo-EEG-guided thermocoagulation has the potential for a promising new treatment option in patients not amenable to resective epilepsy surgery. There is no general consensus on which palliative procedure is most effective in patients with difficult-to-treat epilepsy syndromes. The decision must be based on individual factors of a given patient. This review summarizes experience with palliative approaches collected in adult and pediatric patient series over the past decades and may help to thoroughly balance beneficial effects and risks of each procedure.

Keywords Palliative epilepsy surgery • Corpus callosotomy • Vagal nerve stimulation • Multiple subpial transections • Thermocoagulation • Deep brain stimulation

Introduction

Epilepsy is one of the most common neurological diseases with a prevalence of about 1 % in the world's population. Forty-seven percent of epilepsy patients become seizure-free with the first antiepileptic medication in monotherapy, and an additional 14 % of epilepsy patients will obtain seizure freedom with a second drug in monotherapy. The remaining patients are difficult to treat and often receive polytherapy [59]. Approximately one third of patients do not respond adequately to antiepileptic drugs. Even though many new antiepileptic drugs have been developed during the last 20 years, the percentage of patients with medically intractable epilepsy has not profoundly changed.

A special subgroup of these pharmacoresistent patients with focal epilepsy is amenable to curative epilepsy surgery. However, resective epilepsy surgery cannot be performed in patients in whom no epileptic focus is identifiable or a resection of the epileptogenic focus would imply severe functional impairments (e.g., speech and memory deficits, impairment of motor functions).

Severe and uncurable epilepsy syndromes often manifest in early childhood. In these patients, multifocal or large and often not localizable epileptogenic foci predispose the patient to rapid generalization of epileptic discharges and to harmful tonic or atonic drop attacks. If disabling seizures persist despite optimal medical treatment, several palliative surgical procedures can be proposed with the aim of decreasing seizure frequency and to improve quality of life. Among these procedures, we review disconnective procedures such as corpus callosotomy and multiple subpial transections, various stimulation procedures (vagal nerve stimulation, focus distant deep brain stimulation, hippocampal stimulation, responsive direct cortical stimulation), and stereo-EEG-guided thermocoagulation. For each procedure, the techniques, indications, and outcomes are described.

Detailed Review of the Literature

References for this review were identified by searches of PubMed using the terms "callosotomy," "multiple subpial transection and epilepsy," "vagus nerve stimulation and epilepsy," "brain stimulation and epilepsy," "thermocoagulation and epilepsy," and "palliative surgery and epilepsy" from January 2000 until December 2010. Further articles were identified from the references of the selected studies.

Corpus Callosotomy

History

Corpus callosotomy is the palliative procedure with the longest tradition. It was introduced in 1940 as a palliative treatment option for intractable seizures by Van Wagenen and Herren [126]. In 1975, Wilson et al. [136] were the first to use the operating microscope and developed microsurgical techniques for partial and complete callosotomy. Since then, some details of the surgical techniques have been modified [28, 31, 74, 76]. The rationale of seizure reduction by callosotomy is based on the hypothesis that the corpus callosum is the most important pathway for interhemispheric spread of epileptic activity. A disconnection of both hemispheres by a corpus callosotomy impedes rapid bilateral synchronization of epileptic discharges.

Indications

In general, corpus callosotomy successfully treats a wide variety of seizures and epilepsy syndromes and has been accepted as a palliative surgical procedure for patients with disabling seizures who are not amenable to focal resections.

Tonic and atonic drop attacks are the most common indication for corpus callosotomy [24, 43, 55, 70, 71, 73, 118, 119]. Thus, corpus callosotomy is a treatment option in children with Lennox-Gastaut syndrome comprising tonic, atonic, or tonic-clonic seizures [24, 60, 96, 134]. Further candidates for corpus callosotomy are patients with (a) recurrent episodes of status epilepticus [70, 71], (b) partial (mainly frontal) seizure onset and rapid secondary generalization, (c) no obvious epileptogenic focus, and (d) multifocal or widespread lesions (e.g., tuberous sclerosis, hemimegalencephaly) [55, 65, 70, 99]. Moreover, few publications report a marked benefit in patients with medically refractory idiopathic epilepsy with generalized tonic-clonic and absence of seizures [23, 52].

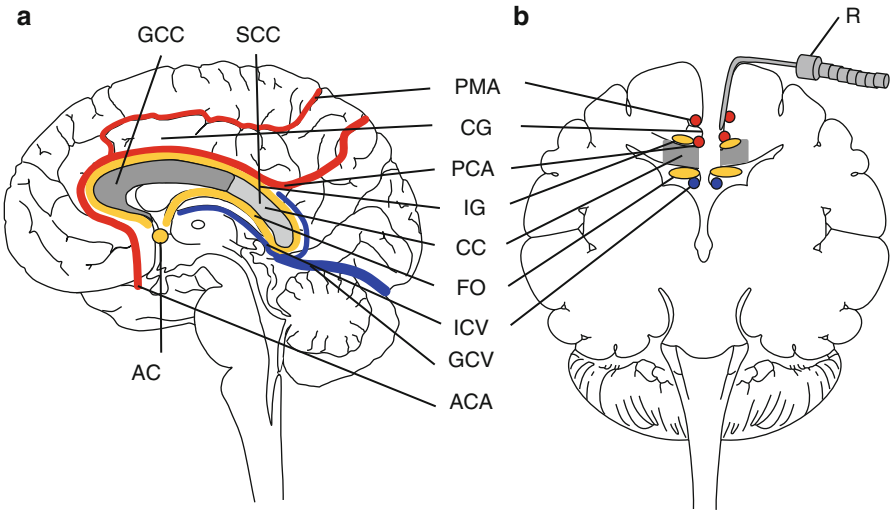

Fig. 1 Illustration of corpus callosotomy. (**a**) Sagittal view of a brain in midline. Anterior two-third callosotomy is indicated in *dark gray*, and posterior one-third callosotomy is indicated in *light gray*. (**b**) The left vertex is gently pushed aside with a self-retaining retractor (*R*). *AC* anterior commissure, *ACA* anterior cerebral artery, *CC* corpus callosum, *CG* cingulate gyrus, *FO* fornix, *GCV* great cerebral vein of Galen, *GCC* genu corporis callosi, *ICV* internal cerebral vein, *IG* indusium griseum, *PCA* pericallosal artery, *PMA* pericallosal marginal artery, *SCC* splenium corporis callosi red color: arteries, blue color: veins, yellow color: nerval structures.

Techniques

At our institution callosotomy is performed as follows: After intubation, the patient is positioned on the operating table with the head fixed in a three-point skeletal fixation. The position is supine with 30° inclination of the head for anterior and complete callosotomy and prone 20° retroflexion of the head for posterior callosotomy. At the time of scalp incision, mannitol (1 g/kg) is administered intravenously. For an anterior callosotomy, a right frontal free bone flap measuring 5 × 5 cm and which runs 1 cm dorsal and 5 cm anterior to the bregma and slightly crosses the midline is fashioned. The corresponding bone flap for a posterior callosotomy measures 6 × 5 cm, extends 1 cm posterior to the lambda and 5 cm anterior to the lambda and slightly crosses the midline. The dura is opened in a curvilinear fashion and reflected to the sagittal sinus. At this point, the operation microscope is used.

While dissecting the interhemispheric fissure, it may be necessary to divide small bridging veins. However, division of larger veins posterior to the bregma is always avoided. The dissection down to the interhemispheric fissure is continued, dividing arachnoidal adhesions that are often encountered, particularly in patients who have an incomplete falx cerebri and at the level of the cingular gyrus, until the corpus callosum is reached (Fig. 1). The corpus callosum is readily distinguished from the overlying cingulate cortex by its glistening, bright white color. The self-retaining retractor is inserted and the pericallosal arteries are identified. Further exposure of the callosum is accomplished following the pericallosal arteries anteriorly as well as

posteriorly. In order to provide sufficient working space between both pericallosal arteries, small arterial vessels supplying the exposed corpus callosum as well as veins are coagulated and divided. Thereafter, the pericallosal arteries are protected with cotton wool and the retractor is adjusted over the protected artery.

Division of the corpus callosum is accomplished using a microsuction device or the cavitron ultrasonic aspirator (CUSA). The dissection is performed in the midline because on the indusium griseum, a commissural hippocampal pathway is located on both lateral surfaces of the corpus callosum. The dissection is carried down to the blue-gray lining that provides a thin barrier and which may be preserved in its integrity. In the anterior procedure, sectioning is first performed forward through the genu and rostrum until the anterior commissure, which is spared, is seen. The anterior commissure is a commissural pathway between both temporal lobes. Thereafter, sectioning of the callosal fibers is extended posteriorly as desired. When partial section is performed, a titanium clip may be placed at the posterior extent of the division to facilitate imaging of that limit and to serve as a surgical marker should a subsequent complete callosotomy be required. If complete callosotomy is intended, division is carried out through the splenium to the tentorial arachnoid until the vein of Galen is seen. While splitting the commissura fornicis, it is essential to keep the midline, thus not jeopardizing the fornix. The interhemispheric fissure is examined throughout its length to assure hemostasis. After closing the dura, the free bone flap is reimplanted, a subgaleal drain is placed, and the scalp is closed conventionally in two layers [141].

Other surgical techniques currently used may differ with respect to positioning of the patient, skin incision, extent of trephination, methods of brain relaxation, and tools used for sectioning the corpus callosum. Recently, radiosurgical callosotomy with gamma knife has been performed [16, 28, 31, 115].

Results

Outcome of Callosotomy

The postoperative outcome is highly dependent on the *seizure types* occurring in a given patient. According to recent studies of larger patient series [24, 43, 70, 118, 119], *drop attacks* best responded to corpus callosotomy: 44–84 % of patients were cured from drop attacks (tonic/atonic) and 80–99 % of patients (including those with cure from this seizure type) had at least a moderate improvement with >50 % seizure reduction. Favorable results were also obtained in patients with *secondarily generalized tonic-clonic seizures*: In 12–57 % of patients secondarily generalized seizures were completely abolished and 46–94 % of patients (including those with cure from this seizure type) showed >50 % seizure reduction. Concerning *atypical absences*, outcome was also quite satisfactory: In 20–82 % of patients, atypical absences completely stopped and 53–90 % of patients (including those with cure from this seizure type) had >50 % seizure reduction. Less impressive results were observed for *complex partial seizures*: 0–22 % of patients were free from complex partial seizures and 20–91 % of patients (including those with cure from this seizure type) had >50 % seizure relief. Also, poorer outcomes are described in *myoclonic seizures*: 0–27 % of patients were seizure free and 27–92 % of patients (including those with cure from this seizure type) had at least >50 % seizure reduction (Tables 1a and 3).

Table 1a Seizure reduction per seizure type after callosotomy

Seizure type	Seizure reduction	Maehara et al. (2001) (52 patients) (%)	Hanson et al. [43] (41 patients) (%)	Cukiert et al. [24] (76 patients) (%)	Sunaga et al. [118] (78 patients) (%)	Tanriverdi et al. [119] (95 patients) (%)
Drop attacks	Cure	80	–	–	84	44
	>50 % reduction	92	80	–	93	99
GTC	Cure	12	–	57	27	50
	>50 % reduction	61	50	57	56	94
Atypical absences	Cure	20	–	49	31	32
	>50 % reduction	53	–	82	72	90
CPS	Cure	0	–	–	14	22
	>50 % reduction	20	57	–	21	91
Myoclonic seizures	Cure	0	–	27	–	27
	>50 % reduction	27	–	73	–	92

Recent publications are listed. Consistently best results are reported in drop attacks and generalized tonic-clonic seizures
GTC generalized tonic-clonic seizures, *CPS* complex partial seizures

Table 1b Seizure reduction per seizure type after VNS in Lennox-Gastaut syndrome

Seizure type	Seizure reduction	Majoie et al. [72] (19 patients) (%)	Kostov et al. [57] (30 patients) (%)
Drop attacks (or tonic/atonic seizures)	Cure	8	24
	>50 % reduction	23	64
GTC	Cure	0	15
	>50 % reduction	10	55
Atypical absences	Cure	10	20
	>50 % reduction	40	60
CPS	Cure	20	0
	>50 % reduction	60	75
Myoclonic seizures	Cure	14	18
	>50 % reduction	57	54

Vagus nerve stimulation had a certain effect on all seizure types without any preference. More favorable results in the study by Kostov et al. may be related to a longer observation period
GTC generalized tonic-clonic seizures, *CPS* complex partial seizures

Apart from the seizure type, the *underlying pathology* may play a role in postoperative outcome. In patients with bilateral malformations of the cortical development such as diffuse cortical dysplasia, tuberous sclerosis and lissencephaly, good surgical results have been reported with callosotomy [113, 119]. In patients with temporal lobe epilepsy, however, complex partial seizures are probably not influenced by anterior callosotomy [98, 113].

The *extent of the corpus callosotomy* also influences the seizure outcome. In several outcome analyses, a complete corpus callosotomy was superior to an anterior two-thirds corpus callosotomy, but the risk of peri- and postoperative complications was also slightly higher with complete callosotomy [49, 52, 55, 100, 118, 119, 123, 138].

Further prognostic factors concerning the postoperative outcome may relate to several *EEG features*. Seizure onset with generalized slow spike-wave complexes, electrodecrement, or low-amplitude fast activity as well as *interictal* slow spike-wave activity was associated with a favorable postoperative outcome. In contrast, interictal EEG recordings revealing bilateral independent spikes have been associated with poor outcome [43].

Several studies report long-term follow-ups in patients with corpus callosotomy [50, 118, 119, 121, 123]. The observation period ranged between 1 and 25 years. All these studies agree that complete seizure freedom after corpus callosotomy is an absolute rarity and is observed in only one reported patient [123]. Considerable improvement (>50 % seizure reduction), in particular concerning the most disabling seizure types, is consistently reported in 60–76 % of patients (Table 2).

In addition to seizure reduction, several studies report improvement in overall daily functions [70, 101, 123]: Changes include improvement in hyperactivity, emotional well-being, speech functions, memory functions, attentiveness, and self-care. Younger age (<18 years) at the time of surgery was an independent predictive factor for improvement in daily functions [70, 123] but not for seizure outcome [6].

Table 2 Comparison of different palliative procedures – outcome

Approach	Percentage of seizure-free patients	Percentage of patients with >50 % seizure reduction	Comments
Callosotomy	Nearly 0	60–76	Large patient series available, considerable reduction of drop attacks and generalized tonic-clonic seizures
MST + cortical resection	42–56	80–88	Seizure relapse in 20 % of patients in a long-term outcome analysis
MST alone	0–15	45–51	Only small patient series available
VNS			Large patient series available
Retrospective studies	0–8	40–64	
Prospective studies	2	23–51	
DBS (ANT) (SANTE study)	13 (at least 6 months)	54	Only significant seizure reduction in temporal lobe CPS
SEEG-guided thermocoagulation	0	54	Only small patient series

Seizure freedom is rarely obtained by palliative procedures. Only MST in combination with cortical resection can be regarded as a curative approach. The main aim of palliative procedures is reduction of the frequency of most disabling seizures and improvement of quality of life
MST multiple subpial transections, *VNS* vagus nerve stimulation, *DBS* deep brain stimulation, *ANT* anterior nucleus of the thalamus, *SEEG* stereoelectroencephalography

Safety Aspects of Callosotomy

Most adverse effects of corpus callosotomy are temporary. Permanent neurological deficits are rare. However, the risk/benefit ratio to such therapy needs to be carefully assessed. Common adverse effects are the following:

*Surgical complication*s: Surgical complications mainly included acute epidural hematoma, hydrocephalus, subdural cerebrospinal fluid accumulation, infections (e.g., meningitis, osteomyelitis), and deep-vein thrombosis, and occurred in 9–20 % of patients [50, 70, 71, 90, 113, 118, 119]. The mortality rate was reported at 2 % in a study from 1977 [137]. Modern techniques yielded lower rates and no deaths were reported in the recent patient series 113.

Permanent neurological deficits: Permanent neurological deficits were caused mainly by trauma, infarction, or intracerebral hemorrhage and occurred in <4 % of patients since the introduction of microsurgical techniques [71, 90].

Disconnection syndrome: Disconnection syndromes are more common with total than with anterior callosotomy. Most patients are unaware of their deficits [55]. Acute disconnection symptoms such as apathy, urinary incontinence, low verbal

output, and hemineglect are very common and usually diminish by time (mean duration 16 days) [24]. Permanent disconnection syndromes are rare (3 %) and to some extent may fluctuate over years [24]. They comprise several phenomena: alien hand syndrome, dichotic listening suppression, tactile dysnomia, hemispatial neglect, nondominant hand agraphia, alexia without agraphia, and tachistoscopic visual suppression (reviewed by Jea et al. [51]). The alien hand syndrome is the most impressive disconnection syndrome, characterized by the phenomenon that the nondominant hand (or leg) acts without guidance of the patient's own will, resulting in complex involuntary movements and intermanual conflicts. Examples are involuntary unbuttoning of clothing, removing objects from tables, throwing objects or even walking in the wrong direction. In addition, apraxia and mutism have been reported.

Memory deficits: Memory deficits are rarely observed and may be related to a section of the hippocampal commissures (fornix and indusium griseum), in particular, by dissection of the splenium, due to the anatomical proximity of the fornix commissure [70, 102].

New types of seizures: The emergence of new varieties of mainly simple partial seizures has been reported [70, 123]. There may be a transient increase in focal seizures immediately after surgery, which typically resolves within 1–2 months.

Multiple Subpial Transection (MST)

History

Based on the observations that a neuronal functional unit is organized vertically [84, 85], the seizures spread horizontally [19, 133], and a minimal contiguous cortical surface area is necessary for the maintenance of cortical activity [69, 103], Morrell et al. [81] suggested a novel technique called multiple subpial transection (MST) in 1989. Vertical transections should theoretically disrupt only horizontally oriented axons and thus the spread of epileptic activity while preserving the vertically oriented architecture and cortical function.

Indications

MST has been developed for surgically intractable epilepsy with seizure foci in primary sensomotor or language areas. MST might be an effective alternative to subtotal resection of the epileptogenic zone in critical brain areas; thus, it has a role when performed in conjunction with cortical resections or lesionectomies [12, 114]. MST as stand-alone therapy, however, may be indicated only in highly selected cases. Moreover, MST has been considered effective for patients with Landau-Kleffner syndrome (LKS) [14, 39, 80].

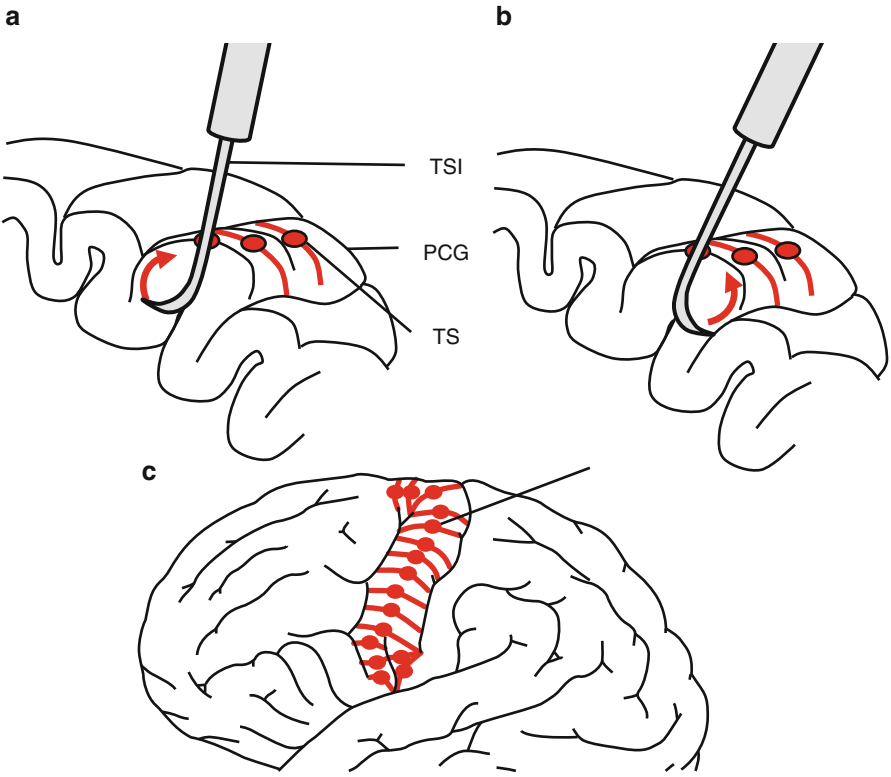

Fig. 2 Illustration of multiple subpial transections. (**a**) Transversal section through the cortex, demonstrating the maneuver with the transection instrument (*TSI*). The precentral gyrus (*PCG*) is entered through a point incision of the pia mater (*red point*); the instrument is gently moved along the curved tip to the opposite side of the gyrus. Thereafter, the transection (*TS*, *red lines*) is carried out by drawing the curved tip backward along the pia mater of the gyrus (**b**). The whole maneuver has to be carried out in a circle-like manner (*red arrows*). (**c**) The transection direction is always vertical against the surrounding sulci

Techniques

MST is conducted according to the technique of Morrell [81]. After bipolar electrocautery of points spaced approximately 5 mm apart along the edge of a given gyrus, the pia mater is sharply incised (Fig. 2). Serial MST are then performed through the incised pial points to a depth of approximately 1.5–2 cm along an axis perpendicular to the gyrus using different hooks. The tip of the knife is visualized through the pia mater as it is drawn back along the subpial space, completing the transection. Care should be taken to avoid disrupting the pia mater or catching sulcal vessels during the transection procedure. In cases wherein MST are performed in multiple contiguous gyri in one or more lobes of the brain, intraoperative ultrasonography can be used at the end of the procedure to ensure that no underlying intracerebral

hematoma was created. Electrocorticography is performed before and after MST to evaluate the interictal activity and response to surgery.

Results

Outcome of MST

Effects of MST on epilepsy are reported in several patient series with variable success. In general, MST performed in combination with resections showed more favorable outcomes than MST alone. According to more recent studies and reviews [8, 12, 47, 91, 97], 42–56 % of patients became seizure-free and in 80–88 % (including seizure-free patients), seizure frequency was considerably reduced (>50 %) when MST was performed in conjunction with cortical resection. However, in the long run (observation periods of 28–89 months after surgery), 19 % of patients sustained an increase in seizure frequency several years after initial postoperative improvement [91] (Table 2).

When MST was conducted as stand-alone therapy, results were less impressive [47, 97, 111]: 0–15 % of patients became seizure-free and 45–51 % (including seizure-free patients) had >50 % seizure reduction. Only one publication [117] reported satisfactory seizure outcomes in selected patients who underwent MST without resection (Table 2).

Multiple subpial transections have been performed in small patient series with Landau-Kleffner syndrome (LKS) (Table 3). Morrell, who first described the procedure, reviewed the experience with 14 patients with LKS who underwent MST. Seventy-nine percent of the patients showed marked improvement in speech and understanding [80]. Similar successful outcomes were reported by Buelow et al. [14] and Grote et al. [39] (1999). Irwin et al. [48] reported on five children with LKS who underwent MST. Language skills improved in all children but none improved to an age-appropriate level. Seizures and behavioral disturbances were immediately ameliorated after the intervention. Cross and Neville [22], reporting on a series of ten patients, found seizure improvement in 50 % of them, 70 % showed language improvement, and some of them had significant behavioral improvement.

Safety Aspects of MST

Transient neurological deficits following MST are frequently observed and are caused by an edema. Transient hemiparesis was seen in around 60 % of patients who underwent MST of the primary motor area and mild to moderate dysphasia in approximately 60 % of patients following MST of the language area [12]. These deficits may persist from 6 weeks to 6 months [12]. Permanent neurological deficits were not or only exceptionally observed in the published patient series [86, 106, 108].

Table 3 Summary of possible indications for palliative procedures in different seizure types and syndromes

	Drop attacks (tonic/atonic)	Myoclonic seizures	Complex partial seizures	Atypical absences	Primarily generalized tonic-clonic seizures	Secondarily generalized tonic-clonic seizures	Malformations of cortical development	Seizures originating from eloquent areas	LGS	LKS
Callosotomy	+++	+	+	++	+	++	+	–	++	–
MST + cortical resection	–	–	–	–	–	–	–	+++	–	–
MST alone								+		+
VNS	+	++	++	+	+	+	(+)	+	+	?
DBS (anterior nucleus of the thalamus)	?	?	+	?	?	?	?	?	?	?

+++, >50 % seizure reduction in >75 % of patients consistently reported in all studies; ++, >50 % seizure reduction in >50 % of patients consistently reported in all studies; +, >50 % seizure reduction in >50 % of patients reported in at least one study; (+) poor or less robust results compared to other indications, *?* effect not known yet

MST multiple subpial transections, *VNS* vagus nerve stimulation, *DBS* deep brain stimulation

Vagus Nerve Stimulation (VNS)

History

The idea of stimulating the vagus nerve to modify central brain activity has been pursued for over 100 years. In 1952, desynchronizing effects of vagal nerve stimulation (VNS) were noted on feline sleep spindles as well as on a strychnine model of epileptiform activity [140]. In 1988, the first stimulator was implanted in a human [95]. VNS therapy received European Community approval in 1994 and US Food and Drug Administration (FDA) approval in 1997. Meanwhile, >50,000 patients have been treated worldwide for epilepsy by VNS therapy. The exact mechanism by which VNS modulates seizures is not known. The vagus nerve projects primarily to the nucleus of the solitary tract, which has projections to multiple areas in the forebrain and brainstem, including areas involved in epileptogenesis such as thalamus, hippocampus, amygdala, and neocortex [107, 132]. It has been postulated that the anticonvulsant effect of VNS may be caused by the release of norepinephrine or its influence on the reticular activating system [58, 77].

Indications

VNS is indicated as an adjunctive therapy for reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures that are refractory to antiepileptic drugs. Meanwhile, many children under 12 years of age with severe epilepsy have been treated off-label [2, 9–11, 25, 26, 27, 29, 36, 37, 42, 45, 57, 88, 112, 124, 131].

Techniques

The patient is positioned supine on the operating table with the head neutral and slightly to moderately extended. The incision is made in a skin crease or fold whenever possible (Fig. 3a). Upon completion of the cervical incision and vagus nerve isolation, either a subcutaneous or a subpectoral approach can be performed. In the subcutaneous approach, the skin incision is made in the left axilla line. A subcutaneous pocket is created directly over the pectoral muscle. In the subpectoral approach [7], the skin incision is made on the lateral border of the pectoralis major, approximately 20 cm below the level of the clavicle along a natural skin crease. The subcutaneous fat layer is then divided with monopolar cautery and with blunt dissection until the lateral border of the pectoralis is visualized. The pectoralis fascia is bluntly divided to the subpectoral fascia, and a pocket is bluntly dissected between the superior and inferior pectoralis fascia. After preparing the pocket, the generator is placed within the pocket to verify the appropriate size of the pocket and resulting skin contour and approximation at the incision. A subcutaneous tunnel is then created from

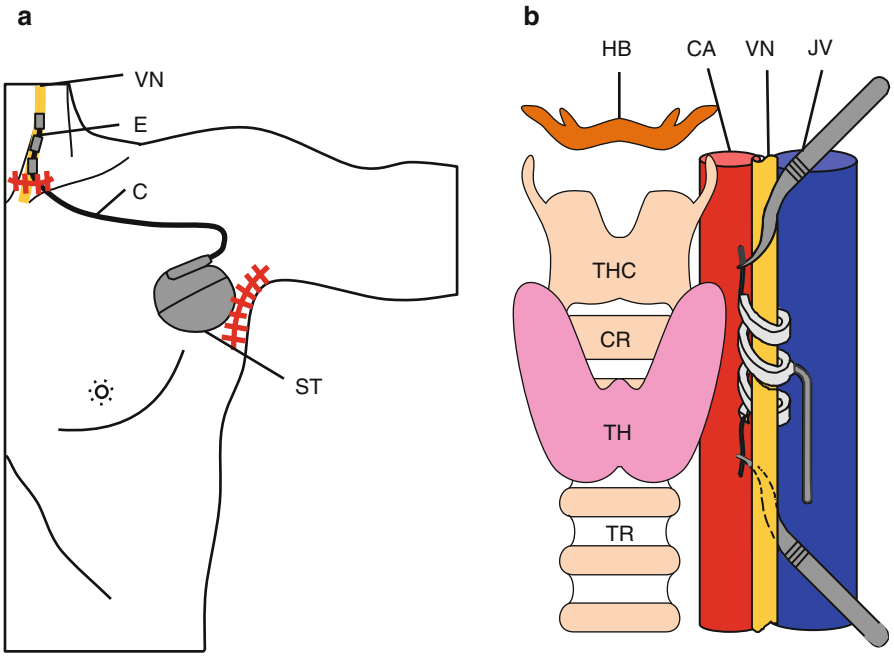

Fig. 3 Illustration of a vagus nerve stimulator implantation. (**a**) Overview of the location of the electrode contacts (*E*) at the vagus nerve (*VN*). The electrodes are connected by a subcutaneous, tunneled cable (*C*) with the stimulator unit (*ST*), which is implanted either subcutaneously or below the pectoral muscle. The *red lines* indicate skin incisions. (**b**) Illustration of the electrode placement along the vagus nerve (*VN*), which is located within a common soft tissue sheet between the carotid artery (*CA*) and jugular vein (*JV*). *CR* cricoid cartilage, *HB* hyoid bone, *TR* trachea, *TH* thyroid gland, *THC* thyroid cartilage

the chest incision to the cervical incision, and the electrode is passed and appropriately positioned around the vagus nerve (Fig. 3b). The cervical skin incision is performed in paramedian between the midline and the border of the sternocleidomastoid muscle below the height of the thyroid cartilage, preferably in a preexisting skin fold. The platysma muscle is prepared and vertically incised. Then the gap between the infrahyal and sternocleidomastoid muscle is bluntly dissected. The common soft tissue sheet of the vagus nerve, carotid artery, and jugular vein is located and incised. The vagus nerve is usually between and behind both vessels. The nerve has to be prepared, with no soft tissue left on the perineurium. Only then can the electrodes be wrapped around the nerve, as shown in Fig. 3b. The electrode wire lead is then secured to the fascia or muscle of the cervical region at two locations and attached to the generator and secured with the set screw. The generator is then placed into the chest pocket and the coil of the remaining lead is placed outside and adjacent to the body of the generator to provide extra length and protection. Thereafter, the generator is tested again to verify that the system's electrical integrity is optimal and that the impedance is within the range for appropriate stimulation function. Finally, the subpectoral or cutaneous pocket and the skin are closed with sutures.

Results

Outcome of VNS

VNS has been proven effective in medically intractable epilepsy. According to many retrospective studies reported between 1999 and 2011 [2, 8–10, 25, 29, 36, 45, 88, 110, 112, 124], 40–64 % of patients have >50 % seizure reduction and 0–8 % of patients became seizure-free. Similar positive results were reported in several registries [3, 61, 104]. Few prospective observational studies and randomized controlled trials [4, 11, 26, 27, 37, 42, 131] have demonstrated >50 % seizure reduction in 23–51 % of patients. According to these studies, approximately 2 % of patients became completely seizure-free (Table 2).

VNS has been reported to be effective in children with Lennox-Gastaut syndrome [36, 45, 57, 72, 105, 112]. In this special patient group, the responder rate (>50 % seizure reduction) was reported in 25–78 % of patients. The high variability may be a result of different group sizes (between 7 and 30 patients per group) and different observation periods. Two studies comprising larger patient numbers report also seizure reduction per seizure type [57, 72]. VNS had a certain effect on all seizure types without any preference to more disabling seizure types. Concerning (tonic and atonic) *drop attacks*, seizure freedom could be achieved in 8–24 % of patients and >50 % seizure reduction was seen in 23–64 % of patients. *Generalized tonic-clonic seizures* were completely abolished in 0–15 % and >50 % seizure reduction was achieved in 10–55 % of patients. *Atypical absences* completely ceased in 10–20 % of patients and >50 % seizure reduction was observed in 40–60 % of patients. *Complex partial seizures* were completely abolished in 0–20 % of patients and >50 % seizure reduction was seen in 60–75 % of patients. *Myoclonic seizures* were completely absent in 14–18 % of patients and >50 % seizure reduction was reported in 54–57 % of patients. The poorer results in the study by Majoie et al. [72] may be related to a relatively short observation period of 6 months (Tables 1b and 3).

Few predictors of VNS efficacy have been consistently reported in the literature. One of the most common and consistent findings is improved seizure control with increasing duration of VNS therapy [3, 27, 38, 45, 61, 87, 94]. Others have reported the following variables as predictors of improved response to VNS: focal epilepsy (eloquent) or temporal lobe epilepsy [29]; fewer failed antiepileptic drugs (AED) [104] higher baseline seizure frequency [62], prior corpus callosotomy [45, 61], higher cognitive function at baseline [1], and focal rather than generalized seizures [61]. Contradictory results were reported as to patient age at implantation [2, 25, 61] and duration of epilepsy [104, 61]. Neuronal migration disorders predicted less robust response to therapy [29].

No negative cognitive side effects have been reported with VNS. Cognition may even improve if concomitant medications can be reduced. VNS therapy promotes alertness [75], improves mood [44], and can provide quality-of-life benefits [30]. VNS may stop or shorten seizures and clusters of seizures and also may improve the postictal period [120].

Safety Aspects of VNS

The placement of a VNS device is a low-risk procedure. Infection may occur at the incision site [116]; the rate of infections is reported between 0 and 8 % (Elliott et al. 2010). There may be paralysis of the vocal cord (usually transient). Significant or permanent injury to the vagus nerve was rare (<4 %) (Elliott et al. 2010). Rarely asystole may occur in the operating room (0.1 %) [109]. Lead fracture or dislodgement from the device and battery failure can occur unrelated to the surgical procedure [45, 116].

In the long run, patients may commonly complain of voice alteration and hoarseness (19–29 %), local paresthesias, throat or neck pain (12 %), and cough (6 %). Dyspnea may be seen (3 %), as well as headaches [18, 42, 56, 83, 87, 116].

Direct and Deep Brain Stimulation for the Treatment of Epilepsy

History

For decades, the effects of electrical stimulation on brain activity have been studied. Direct stimulation of the cerebellum was reported to be effective in treating epilepsy in noncontrolled studies [21], but subsequent controlled studies in a total of 17 patients failed to show significant effects [125, 139]. Early investigations of the thalamus in animal models of epilepsy demonstrated the potential for disruption of seizures induced by both pharmacological and electrical stimulation [78, 79]. Thus, focus distant brain stimulation is supposed to modulate and/or disrupt epileptic activity in larger networks (e.g., in the circuit of Papez). Direct stimulation of the epileptogenic focus may abort epileptic discharges or chronically increase the threshold for epileptic activity.

Indications

Direct brain stimulation may be a treatment option for patients with bilateral or multiple seizure foci as well as for patients with seizure foci in eloquent brain areas. As with any new therapy, identification of ideal candidates remains challenging.

Thalamic stimulation for the treatment of epilepsy has been performed in the centromedian nucleus (Fig. 4a, [33, 127, 130]) and the anterior nucleus of the thalamus (Fig. 4b, [5, 32, 46, 54, 66, 92]).

First data from a multicenter, double-blind, randomized trial [32] showed that bilateral stimulation of the anterior nuclei of the thalamus (SANTE, Fig. 4b) is most effective in patients with temporal lobe epilepsy as opposed to extratemporal, neocortical epilepsy. Statistically significant improvement was noted in complex partial seizures (Table 3).

Deep brain stimulation (DBS) of the substantia nigra pars reticulata and the subthalamic nucleus may be an effective treatment option for patients with progressive myoclonic epilepsy in adulthood as shown in a small patient group [135].

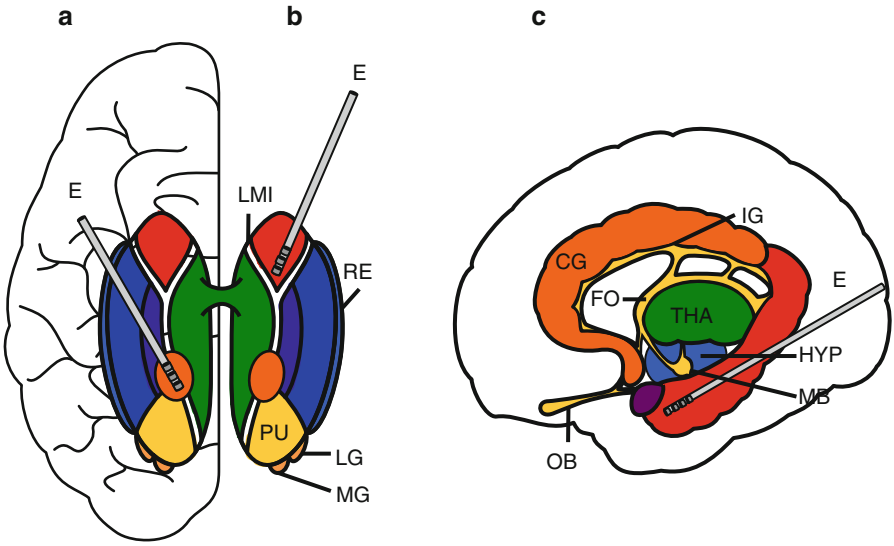

Fig. 4 Illustration of deep brain stimulation. (**a**) Overview of the locations of electrode (*E*) targets in thalamic stimulation in the centromedian nucleus (*CE*) or in the (**b**) anterior thalamic nucleus (*AN*). For anatomical orientation, other marked thalamic structures are the medial- (*ME*), ventral- (*VE*), lateral- (*LA*), pulvinar- (*PU*), lateral geniculate- (*LG*), medial geniculate (*MG*) nucleus and lamina medullaris interna (*LMI*). (**c**) Electrode (*E*) placement in hippocampal (*H*) stimulation. *A* amygdala, *CG* cingulate gyrus, *FO* fornix, *HYP* hypothalamus, *IG* indusium griseum, *MB* mammillary body, *OB* olfactory bulb, *THA* thalamus

Techniques

The procedure for electrode implantation begins with placement of the stereotactic frame under general anesthesia. After placement of an MRI localizer grid, fast spin echo inversion recovery and standard T2 high-resolution, 1-mm slice images are obtained for targeting. Computed tomography may also be a reasonable alternative for stereotactic localization. Indirect localization of the desired target can be obtained with reference to a standard stereotactic atlas by identifying the anterior and posterior commissures on axial images. Frame position relative to the AC-PC line is calculated. Direct radiographic identification of the target is also possible for most potential DBS targets, including the anterior thalamic nucleus, the subthalamic nucleus, the caudate, and the hippocampus.

The patient is fixed in a Mayfield head frame in a supine or a semisitting position. Head position is altered to optimize access to the chosen entry point. A burr hole is placed and the dura and pia are sharply incised and cauterized with care to avoid surface vessels. A guide cannula is inserted under neuronavigation from an MRI dataset. The cannula position is confirmed with fluoroscopy. A monopolar single-unit recording electrode can be introduced and used for confirmation of the targeted thalamic nucleus by recording the specific firing pattern. For targeting the anterior thalamic nucleus (AN), the lateral ventricle is invariably traversed and no unit

recordings are made here. Recordings are first heard in the superficial surface of the AN. For the AN, the electrode is advanced further until recordings cease as the electrode enters the intralaminar region (Fig. 4b, LMI), in which the characteristic firing pattern ceases because the white matter generates no signal. Recordings with a different firing pattern resume as the electrode enters the dorsomedial nucleus of the thalamus (Fig. 4b, ME). For AN specifically, an additional step is used to confirm lead placement using characteristic EEG activity following frequency stimulation. Stimulation parameters include a frequency of 5–10 cycles/s with a pulse width of 90–330 μs, a pulse amplitude of 4–5 V, and total pulse duration between 3 and 10 s. Stimulation at these frequencies in the AN is associated with recruiting rhythms on the cortical EEG.

Following confirmation of EEG activity and removal of the lead, the final DBS lead is inserted. Fluoroscopy is again used to confirm electrode placement. The electrode is secured with a burr hole cap and the skin incision is closed. The same sequence of steps is used for placing the contralateral electrode. The internal pulse generator is placed the same day or 1 day later. The scalp incisions are opened and the electrode wires are identified and connected to an extension wire. These are tunneled subcutaneously to an infraclavicular position, as described in the VNS section above (Fig. 3a). Postoperatively, lead placement is confirmed with MRI or CT [63].

Results

Outcome of Direct Brain Stimulation

1. *Focus distant brain stimulation*:
   Cerebellar stimulation: A double-blind, randomized controlled pilot study of bilateral stimulation of the superomedial cerebellar cortex in five patients with medically refractory motor seizures found a significant reduction of tonic-clonic and tonic seizures over 6 months. Generalized tonic-clonic seizures were reduced after 1–2 months and continued to decrease over the first 6 months. The effect was stable over the study period of 2 years and beyond [129].

   Thalamic stimulation: Thalamic stimulation for treatment of epilepsy has been performed in the centromedian nucleus [33, 127, 130] and the anterior nucleus of the thalamus [5, 32, 46, 54, 66, 92].

   Stimulation of the *centromedian nucleus of the thalamus* has shown limited effect in humans with epilepsy: Chronic, bilateral 60-Hz stimulation of the centromedian nucleus of the thalamus in 13 patients reduced primary and secondary generalized tonic-clonic seizures but had no effect on complex partial seizures [130]. A pilot, uncontrolled nonblinded trial using continuous stimulation of the centromedian nucleus in seven patients reported significant improvement in only one patient [33].

   The *anterior nucleus of the thalamus* is an attractive target because of its close connections to the mesial temporal structures via the fornix, mammillothalamic tracts, and thalamocortical radiations. Several uncontrolled trials yielded varying

results: In a publication by Andrade et al. [5], five of six patients had >50 % seizure reduction. A microthalamotomy effect on seizure expression by implantation of the electrodes alone without stimulation was suggested. In another pilot study, all four investigated patients showed >50 % seizure reduction. Lim et al. [66] investigated four patients and only one of them had a seizure reduction >50 %.

A large multicenter, double-blind, randomized trial using bilateral stimulation of the anterior nuclei of thalamus (SANTE) confirmed effectiveness (Tables 2 and 3). By 2 years, there was a 56 % median reduction in seizure frequency; 54 % of patients had a seizure reduction of >50 %, and 13 % of patients were seizure-free for at least 6 months. Patients with seizures arising from the temporal lobe(s) ($n=66$) had a significant reduction in seizure frequency compared to baseline, whereas those with frontal ($n=30$), parietal ($n=5$), or occipital ($n=4$) onsets did not demonstrate significant reduction.

Nucleus subthalamicus: The stimulation of the *subthalamic nucleus* acts via modulation of the "dorsal midbrain anticonvulsant zone." Small open-label trials have reported seizure reduction in some patients treated with this technique [17, 67]. The effect, however, seemed not to be strong enough in order to continue stimulation of the subthalamic nucleus in larger clinical studies under the stimulation parameters applied so far.

Interestingly, deep brain stimulation of the substantia nigra pars reticulata and the subthalamic nucleus may be an effective treatment option for patients with progressive myoclonic epilepsy in adulthood [135]. In all five patients in that study, significant reduction of myoclonic seizures was observed ranging between 30 and 100 %.

2. *Direct stimulation of the epileptogenic focus*:
Hippocampal stimulation: Treating temporal lobe epilepsy with stimulation seems to be attractive as it could potentially avoid memory deficits associated with surgery. Moreover, both hippocampi can be stimulated (Fig. 4c).

Uncontrolled studies with good responder rates in patients receiving continuous stimulation have been conducted as proof of principle [13, 122, 128]. Favorable results were demonstrated by Velasco et al. [128] (all nine patients were responders with >50 % seizure reduction) and by Boon et al. [13] (seven of ten patients were responders with >50 % seizure reduction). However, in the study by Tellez-Zenteno et al. [122], only one of five patients experienced >50 % seizure reduction.

Currently, larger systematic controlled studies of scheduled stimulation of the mesial temporal structures are under way (CoRaStir = prospective randomized controlled study of neurostimulation in the medial temporal lobe for patients with medial temporal lobe epilepsy; MET-TLE = randomized controlled trial of hippocampal stimulation for temporal lobe epilepsy).

Responsive cortical stimulation: Responsive neurostimulation is based on the concept that brief bursts inhibit after-discharges [20, 53, 64]. The ideal treatment scenario of responsive stimulation includes detection of an electrographic seizure by depth or cortical strip electrodes in the seizure zone before the onset of clinical symptoms. An electrical stimulus (short pulse of high-frequency stimulation) aborts the electrographic seizure and, therefore, prevents clinical symptoms. The

feasibility of such devices has been demonstrated in 65 patients in whom electrodes were implanted [82]. Another feasibility study performed by a single center described a 45 % decrease in seizures in seven of eight patients with a mean follow-up of 9 months [35]. A larger pivotal double-blind controlled trial for responsive neurostimulation was performed in 109 patients; results are pending.

Responsive neurostimulation is challenging for mainly two reasons: (1) Patient-specific algorithms must be defined in order to detect early epileptiform activity in a given patient. (2) In case of incomplete stimulation of the seizure onset zone, epileptic activity may propagate from not preserve areas and expand over the whole brain.

Safety aspects of direct brain stimulation: Most common adverse effects in stimulation of the *anterior nuclei of the thalamus* are as follows:

(a) *Device-related adverse events*:
Paresthesias (18.2 %), pain at implantation site (10.9 %), and infections (12.7 %) were most commonly seen. Asymptomatic hemorrhages were noted in 4.5 % patients. Both depression and memory complaints were significantly higher in the stimulation group compared to the control group [32]. Kerrigan et al. [54] reported a 5 % risk of infection and a 5–7.5 % risk of intracerebral hemorrhage leading to clinical symptoms.

(b) *Epilepsy-related complications*:
Six percent of patients experienced new seizure types and 9 % of patients had an increase in seizure frequency compared to baseline. In 5 % of patients status epilepticus occurred: in two patients following implantation, in one patient following the initiation of stimulation after the blinded phase, and in one patient following discontinuation of stimulation. One percent of patients experienced simple partial seizures corresponding to the stimulation cycle following initiation of stimulation [32].

Most common adverse effects of *responsive neurostimulation studies* included device-related events reported in 9 % of patients, such as infections, skin erosion, cranial reconstruction, and increased seizures, all of which resolved [82]. In another responsive neurostimulation feasibility study, no serious device-related adverse event was observed [35].

One safety concern that still remains is that chronic subthreshold stimulation may induce neural injury. Experience with deep brain stimulation for patients with Parkinson's disease, however, suggests that chronic stimulation can be delivered safely [41].

SEEG-Guided Thermocoagulation

History

Developed in the 1960s for the treatment of behavioral disorders [89], stereotactic radiofrequency thermocoagulation (RFTC) lesioning was proposed for treatment of

drug-resistant temporal lobe epilepsy by producing lesions in the amygdala-hippocampus structures [34]. The outcome of stereotactic RFTC targeted on a selected structure such as the amygdala or hippocampus proved definitively less favorable than that of standard surgery [93]. In recent years, the efficacy of this method has been improved by aiming at a tailored (total or partial) destruction of the epileptogenic zone using SEEG guidance [40].

Indications

Thermocoagulation may be a treatment option for patients in whom stereoelectroencephalography (SEEG) is used for invasive video-EEG monitoring and who are not eligible for surgery because of multiple epileptogenic foci or because of the vicinity of the epileptogenic focus with respect to eloquent areas.

Techniques

The procedure is performed without anesthesia. Lesions are made using a radiofrequency lesion generator system (Radionics Medical Products, Burlington, MA) connected to the SEEG electrodes (Dixi Medical, Besancon, France). The lesions are produced between two contiguous contacts of the selected electrodes. Temperature cannot be monitored in vivo at the electrode contacts, so the lesions are made using a 50-V, 120-mA current, which was found in vitro to increase the local temperature to 78–82 °C within a few seconds. A depth EEG recording is performed for at least 5 min before and after the RFTC procedure between the two contacts used for RFTC as well as at all contacts located on the same electrode. The choice of targets depends on data from video-SEEG recordings. Criteria are low-amplitude fast-activity pattern or spike-wave discharges at onset of seizures and no clinical response to stimulation (noneloquent areas) [15].

Results

Outcome of Thermocoagulation

SEEG-guided RFTC showed a favorable benefit/risk ratio in a case series of 13 patients in whom surgery was risky or not feasible. Seven of these patients (54 %) benefited from RFTC, with a reduction of >50 % in seizure frequency [15]. Best results were obtained in patients with malformations of the cortical development (dysplasia and heterotopia) [68, 15] (Table 2).

Conversely, results of RFTC in patients eligible for lesionectomy are clearly inferior to those of surgery. Thus, SEEG-guided RFTC is not recommended as an alternative to resective surgery.

Safety Aspects of Thermocoagulation

In the above-mentioned case series, complications were rare. No permanent neurological or cognitive impairment occurred after any procedure. Three of 43 patients showed transient adverse effects. Dysesthesia of the mouth occurred following intrainsular RFTC in two patients, and motor apraxia in the left hand occurred following RFTC in the right supplementary motor area in one patient [15].

Summary, Conclusions and Proposals for the Future

Several surgical options exist for patients with medically intractable epilepsy in whom the epileptogenic focus cannot be surgically removed and in whom very disabling seizures persist despite optimal pharmacotherapy. These techniques allow a reduction of seizure frequency but do not cure the patient. The first-line aim is to ameliorate quality of life. The choice of the individually adequate palliative procedure depends on several factors. A thorough risk/benefit assessment is necessary and several points should be taken into consideration.

First, evidence base and experience concerning outcomes and long-term effects vary remarkably among the different palliative approaches. Corpus callosotomy and VNS have been performed in large patient series and long-term follow-up analyses are available. For VNS, randomized and double-blinded trials exist. Deep brain stimulation, on the other hand, is an emerging treatment option for medically intractable epilepsy. The best targets and modes of stimulation are still under investigation. Larger, more well-controlled studies are necessary.

Second, the most disabling seizure types, epilepsy syndromes, or other patient-specific characteristics should be considered when deciding on the best palliative surgical technique. Tables 1a, b, 2, and 3 summarize different seizure types and epilepsy syndromes and the respective responsiveness to different palliative surgical techniques reported in the literature during the past 10 years (Tables 1a and b: seizure reduction per seizure type in corpus callosotomy and VNS; Table 2: seizure outcome in general after different approaches; Table 3: possible indications for palliative procedures depending on the leading seizure type or underlying syndrome). Moreover, some palliative procedures are suitable only for highly selected patient groups such as SEEG-guided thermocoagulation for patients undergoing invasive video-SEEG monitoring and MST for patients with an epileptogenic focus in eloquent brain areas.

Third, the invasiveness of alternative palliative procedures varies considerably. The implantation of a VNS is a low-risk procedure compared to a corpus callosotomy. Anterior corpus callosotomy is less frequently associated with chronic disconnection syndromes than is complete corpus callosotomy; however, it is also less effective in reducing seizure severity and frequency. In patients with Lennox-Gastaut syndrome, for example, VNS and anterior or complete callosotomy are potentially alternative therapies. Identifying suitable candidates for each procedure remains challenging.

The decision is based on mainly individual criteria, a general consensus does not exist. Important individual features of the patients include the most disabling seizure type(s), the urge for immediate improvement (how many drop attacks? how many generalized tonic-clonic seizures?), presumed quality of life, intellectual performance, and the age of the patient. In some patients a two-step procedure is justified, beginning with a low-risk procedure and then, in case of failure, therapy with higher risks. It should be taken into consideration that it takes time for the maximal anticonvulsive effect of VNS to be seen. Procedures with a higher perioperative risk or risk of postoperative prolonged or permanent neurologic deficits are only legitimate if seizure outcome is supposed to be superior to less invasive procedures. This has been shown for complete corpus callosotomy versus anterior corpus callosotomy and is supposed for callosotomy versus VNS with respect to drop attacks and generalized tonic-clonic seizures.

The establishment of new therapeutic strategies such as deep/direct brain stimulation in medically intractable epilepsy is a most intriguing topic and will depend mainly on the proof of equality or superiority to well-known palliative procedures. Finally, cost-effectiveness (in particular that of individually tailored devices for responsive cortical stimulation) will not be just a marginal factor in the acceptance of these new therapeutic strategies.

Acknowledgements We thank Dr. Thomas Freiman, Department of Neurosurgery, University of Freiburg, Freiburg, Germany, for providing the Figures 1 to 4.

References

1. Aldenkamp AP, Majoie HJ, Berfelo MW, Evers SM, Kessels AG, Renier WO, Wilmink J (2002) Long-term effects of 24-month treatment with vagus nerve stimulation on behavior in children with Lennox-Gastaut syndrome. Epilepsy Behav 3:475–479
2. Alexopoulos AV, Kotagal P, Loddenkemper T, Hammel J, Bingaman WE (2006) Long-term results with vagus nerve stimulation in children with pharmacoresistant epilepsy. Seizure 15:491–503
3. Amar AP, Apuzzo ML, Liu CY (2004) Vagus nerve stimulation therapy after failed cranial surgery for intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry. Neurosurgery 55:1086–1093
4. Amar AP, DeGiorgio CM, Tarver WB, Apuzzo ML (1999) Long-term multicenter experience with vagus nerve stimulation for intractable partial seizures: results of the XE5 trial. Stereotact Funct Neurosurg 73:104–108
5. Andrade DM, Zumsteg D, Hamani C, Hodaie M, Sarkissian S, Lozano AM, Wennberg RA (2006) Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy. Neurology 66:1571–1573
6. Asadi-Pooya AA, Sharan A, Nei M, Sperling MR (2008) Corpus callosotomy. Epilepsy Behav 13:271–278
7. Bauman JA, Ridgway EB, Devinsky O, Doyle WK (2006) Subpectoral implantation of the vagus nerve stimulator. Neurosurgery 58(4 Suppl 2):ONS-322-5; discussion ONS-325-6
8. Benifla M, Otsubo H, Ochi A, Snead OC 3rd, Rutka JT (2006) Multiple subpial transection in pediatric epilepsy: indications and outcomes. Childs Nerv Syst 22:992–998
9. Benifla M, Rutka JT, Logan W, Donner EJ (2006) Vagal nerve stimulation for refractory epilepsy in children: indications and experience at the Hospital for Sick Children. Childs Nerv Syst 22:1018–1026

10. Ben-Menachem E, Hellstrom K, Waldton C, Augustinson LE (1999) Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years. Neurology 52:1265–1267
11. Ben-Menachem E, Manon-Espaillat R, Ristanovic R, Wilder BJ, Stefan H, Mirza W, Tarver WB, Wernicke JF, for the First International Vagus Nerve Stimulation Study Group (1994) Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. Epilepsia 35:616–626
12. Blount JP, Langburt W, Otsubo H, Chitoku S, Ochi A, Weiss S, Snead OC, Rutka JT (2004) Multiple subpial transections in the treatment of pediatric epilepsy. J Neurosurg 100:118–124
13. Boon P, Vonck K, De Herdt V, Van Dycke A, Goethals M, Goossens L, Van Zandijcke M, De Smedt T, Dewaele I, Achten R, Wadman W, Dewaele F, Caemaert J, Van Roost D (2007) Deep brain stimulation in patients with refractory temporal lobe epilepsy. Epilepsia 48:1551–1560
14. Buelow JM, Aydelott P, Pierz DM, Heck B (1996) Multiple subpial transection for Landau-Kleffner syndrome. AORN J 63:727–729, 732–735, 737–739, 741–744
15. Catenoix H, Mauguiere F, Guenot M, Ryvlin P, Bissery A, Sindou M, Isnard J (2008) SEEG-guided thermocoagulation: a palliative treatment of nonoperable partial epilepsies. Neurology 71(21):1719–1726
16. Celis MA, Moreno-Jiménez S, Lárraga-Gutiérrez JM, Alonso-Vanegas MA, García-Garduño OA, Martínez-Juárez IE, Fernández-Gónzalez MC (2007) Corpus callosotomy using conformal stereotactic radiosurgery. Childs Nerv Syst 23:917–920
17. Chabardes S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid AL (2002) Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. Epileptic Disord 4(Suppl 3):S83–S93
18. Charous SJ, Kempster G, Manders E, Ristanovic R (2001) The effect of vagal nerve stimulation on voice. Laryngoscope 111:2028–2031
19. Chervin RD, Pierce PA, Connors BW (1988) Periodicity and directionality in the propagation of epileptiform discharges across neocortex. J Neurophysiol 60:1695–1713
20. Chkhenkli SA, Sramaka M, Lortkipandize GS, Rakviashvili TN, Bregvadze ES, Magalashvili GE, Gagoshidze TS, Chkhenkeli IS (2004) Electrophysiological effects and clinical results of direct brain stimulation for intractable epilepsy. Clin Neurol Neurosurg 106:318–329
21. Cooper IS, Amin I, Gilman S (1973) The effect of chronic cerebellar stimulation upon epilepsy in man. Trans Am Neurol Assoc 98:192–196
22. Cross JH, Neville BG (2009) The surgical treatment of Landau-Kleffner syndrome. Epilepsia 50(Suppl 7):63–67
23. Cukiert A, Burattini JA, Mariani PP, Cukiert CM, Sárgentoni-Baldochi M, Baise-Zung C, Fortser CR, Mello VA (2009) Outcome after extended callosal section in patients with primary idiopathic generalized epilepsy. Epilepsia 50(6):1377–1380
24. Cukiert A, Burattini JA, Mariani PP, Câmara RB, Seda L, Baldauf CM, Argentoni M, Baise-Zung C, Forster CR, Mello VA (2006) Extended, one-stage callosal section for treatment of refractory secondarily generalized epilepsy in patients with Lennox-Gastaut and Lennox-like syndromes. Epilepsia 47:371–374
25. De Herdt V, Boon P, Ceulemans B, Hauman H, Lagae L, Legros B, Sadzot B, Van Bogaert P, van Rijckevorsel K, Verhelst H, Vonck K (2007) Vagus nerve stimulation for refractory epilepsy: a Belgian multicenter study. Eur J Paediatr Neurol 11:261–269
26. DeGiorgio C, Heck C, Bunch S, Britton J, Green P, Lancman M, Murphy J, Olejniczak P, Shih J, Arrambide S, Soss J (2005) Vagus nerve stimulation for epilepsy: randomized comparison of three stimulation paradigms. Neurology 65:317–319
27. DeGiorgio CM, Schachter SC, Handforth A, Salinsky M, Thompson J, Uthman B, Reed R, Collins S, Tecoma E, Morris GL, Vaughn B, Naritoku DK, Henry T, Labar D, Gilmartin R, Labiner D, Osorio I, Ristanovic R, Jones J, Murphy J, Ney G, Wheless J, Lewis P, Heck C (2000) Prospective long-term study of vagus nerve stimulation for the treatment of refratory seizures. Epilepsia 41:1195–1200
28. Eder HG, Feichtinger M, Pieper T, Kurschel S, Schroettener O (2006) Gamma knife radiosurgery for callosotomy in children with drug-resistant epilepsy. Childs Nerv Syst 22:1012–1017
29. Elliott RE, Morsi A, Kalhorn SP, Marcus J, Sellin J, Kang M, Silverberg A, Rivera E, Geller E, Carlson C, Devinsky O, Doyle WK (2011) Vagus nerve stimulation in 436 consecutive

patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. Epilepsy Behav 20:57–63
30. Ergene E, Behr PK, Shih JJ (2001) Quality-of-life assessment in patients treated with vagus nerve stimulation. Epilepsy Behav 2:284–287
31. Feichtinger M, Schröttner O, Eder H, Holthausen H, Pieper T, Unger F, Holl A, Gruber L, Körner E, Trinka E, Fazekas F, Ott E (2006) Efficacy and safety of radiosurgical callosotomy: a retrospective analysis. Epilepsia 47:1184–1191
32. Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, Oommen K, Osorio I, Nazzaro J, Labar D, Kaplitt M, Sperling M, Sandok E, Neal J, Handforth A, Stern J, DeSalles A, Chung S, Shetter A, Bergen D, Bakay R, Henderson J, French J, Baltuch G, Rosenfeld W, Youkilis A, Marks W, Garcia P, Barbaro N, Fountain N, Bazil C, Goodman R, McKhann G, Babu Krishnamurthy K, Papavassiliou S, Epstein C, Pollard J, Tonder L, Grebin J, Coffey R, Graves N, SANTE Study Group (2010) Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 51(5):899–908
33. Fisher RS, Uematsu S, Krauss G, Cysyk BJ, McPherson R, Lesser RP, Gordon B, Schwerdt P, Rise M (1992) Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 33:841–851
34. Flanigin HF, Nashold BS (1976) Stereotactic lesions of the amygdala and hippocampus in epilepsy. Acta Neurochir 23:235–239
35. Fountas KN, Smith JR, Murro AM, Politsky J, Park YD, Jenkins PD (2005) Implantation of a closed-loop stimulation in the management of medically refractory focal epilepsy: a technical note. Stereotact Funct Neurosurg 83:153–158
36. Frost M, Gates J, Helmers SL, Wheless JW, Levisohn P, Tardo C, Conry JA (2001) Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. Epilepsia 42:1148–1152
37. George R, for the Vagus Nerve Stimulation Study Group (1995) A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurology 45:224–230
38. George R, Salinsky M, Kuzniecky R, Rosenfeld W, Bergen D, Tarver WB, Wernicke JF, for the First International Vagus Nerve Stimulation Study Group (1994) Vagus nerve stimulation for treatment of partial seizures: 3. Long-term follow-up on first 67 patients exiting a controlled study. Epilepsia 35:637–643
39. Grote CL, Van Slyke P, Hoeppner JA (1999) Language outcome following multiple subpial transections for Landau-Kleffner syndrome. Brain 122:561–566
40. Guenot M, Isnard J, Ryvlvlin P, Fischer C, Mauguiere F, Sindou M (2004) SEEG-guided RF thermocoagulation of epileptic foci: feasibility, safety, and preliminary results. Epilepsia 45:1368–1374
41. Haberler C, Alesch F, Mazal P, Pilz P, Jellinger K, Pinter MM, Hainfellner JA, Budka H (2000) No tissue damage by chronic deep brain stimulation in Parkinson's disease. Ann Neurol 48:372–376
42. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilmartin RC, Labar DR, Morris GL 3rd, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW (1998) Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 51:48–55
43. Hanson RR, Risinger M, Maxwell R (2002) The ictal EEG as a predictive factor for outcome following corpus callosum section in adults. Epilepsy Res 49:89–97
44. Harden CL, Pulver MC, Radvin LD, Nikolov B, Halper JP, Labar DR (2000) A pilot study of mood in epilepsy patients treated via vagus nerve stimulation. Epilepsy Behav 1:93–99
45. Helmers SL, Whenless JW, Frost M, Gates J, Levisohn P, Tardo C, Conry JA, Yalnizoglou D, Madsen JR (2001) Vagus nerve stimulation therapy in pediatric patients with refractory epilepsy: a retrospective study. J Child Neurol 16:843–848
46. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43:603–608
47. Hufnagel A, Zentner J, Fernandez G, Wolf HK, Schramm J, Elger CE (1997) Multiple subpial transection for control of epileptic seizures: effectiveness and safety. Epilepsia 38:678–688

48. Irwin K, Birch V, Lees J, Polkey C, Alarcon G, Binnie C, Smedley M, Baird G, Robinson RO (2001) Multiple subpial transections in Landau-Kleffner syndrome. Dev Med Child Neurol 43:248–252
49. Jalilian L, Limbrick DD, Steger-May K, Johnston J, Powers AK, Smyth MD (2010) Complete versus anterior two-third corpus callosotomy in children. Analysis of outcome. J Neurosurg Pediatr 6:257–266
50. Jea A, Vachhrajani S, Johnson KK, Rutka JT (2008) Corpus callosotomy in children with intractable epilepsy using frameless stereotactic neuronavigation: 12-year experience at the Hospital for Sick Children in Toronto. Neurosurg Focus 25:E7
51. Jea A, Vachhrajani S, Widjaja E, Nilsson D, Raybaud C, Shroff M, Rutka JT (2008) Corpus callosotomy in children and the disconnection syndromes: a review. Childs Nerv Syst 24:685–692
52. Jenssen S, Sperling MR, Tracy JI, Nei M, Joyce L, David G, O'Connor M (2006) Corpus callosotomy in refractory idiopathic generalized epilepsy. Seizure 15:621–629
53. Jobst BC, Darcey T, Bujarski KA, Thandani VM, Roberts DW (2009) Application of brief electrical pulses in the primary motor and supplementary motor cortex for the termination of after discharges. Epilepsia 50:2
54. Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, Dichter M, Shetter A, Baltuch G, Jaggi J, Krone S, Brodie M, Rise M, Graves N (2004) Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia 45:346–354
55. Kim DS, Yang KH, Kim TG, Chang JH, Chang JW, Choi JU, Lee BI (2004) The surgical effect of callosotomy in the treatment of intractable seizures. Yonsei Med J 45:233–240
56. Kirse DJ, Werle AH, Murphy JV, Eyen TP, Bruegger DE, Hornig GW, Torkelson RD (2001) Vagus nerve stimulator implantation in children. Arch Otolaryngol Head Neck Surg 128:1263–1268
57. Kostov K, Kostov H, Tauboll E (2009) Long-term vagus nerve stimulation in the treatment of Lennox-Gastaut syndrome. Epilepsy Behav 16:321–324
58. Krahl SE, Clark KB, Smith DC, Browning RA (1998) Locus coeruleus lesions suppress the seizure-attenuating effect of vagus nerve stimulation. Epilepsia 39:709–714
59. Kwan P, Brodie MJ (2000) Early identification of refractory epilepsy. N Engl J Med 342:314–319
60. Kwan SY, Lin JH, Wong TT, Chang KP, Yiu CH (2006) A comparison of seizure outcome after callosotomy in patients with Lennox-Gastaut syndrome and positive or negative history of West syndrome. Seizure 15:552–557
61. Labar D (2004) Vagus nerve stimulation for 1 year in 269 patients on unchanged antiepileptic drugs. Seizure 13:392–398
62. Labar D, Murphy J, Tecoma E, for the E04 VNS Study Group (1999) Vagus nerve stimulation for medication-resistant generalized epilepsy. Neurology 52:1510–1512
63. Lega BC, Halpern CH, Jaggi JL, Baltuch GH (2010) Deep brain stimulation in the treatment of refractory epilepsy: update on the current data and future directions. Neurobiol Dis 38:354–360
64. Lesser RP, Kim SH, Beyderman L, Miglioretti DL, Webber WR, Bare M, Cysyk B, Krauss G, Gordon B (1999) Brief bursts of pulse stimulation terminate after discharges caused by cortical stimulation. Neurology 53:2073–2081
65. Liang S, Li A, Jiang H, Meng X, Zhao M, Zhang J, Sun Y (2010) Anterior corpus callosotomy in patients with intractable generalized epilepsy and mental retardation. Stereotact Funct Neurosurg 88:246–252
66. Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, Chen JL, Chang HW, Su YC, Wu T (2007) Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. Epilepsia 48:342–347
67. Loddenkemper T, Pan A, Neme S, Baker KB, Rezai AR, Dinner DS, Montgomery EB Jr, Lüders HO (2001) Deep brain stimulation in epilepsy. J Clin Neurophysiol 18:514–532

68. Lüders H, Schuele S (2006) Epilepsy surgery in patients with malformations of cortical development. Curr Opin Neurol 19:169–174
69. Lueders H, Bustamante LA, Zablow L, Goldensohn ES (1981) The independence of closely spaced discrete experimental spike foci. Neurology 31:846–851
70. Maehara T, Shimizu H (2001) Surgical outcome of corpus callosotomy in patients with drop attacks. Epilepsia 42:67–71
71. Maehara T, Shimizu H, Oda M, Arai N (1996) Surgical treatment of children with intractable epilepsy. Neurol Med Chir (Tokyo) 36:306–309
72. Majoie HJ, Berfelo MW, Aldenkamp AP, Evers SM, Kessels AG, Renier WO (2001) Vagus nerve stimulation in children with therapy-resistant epilepsy diagnosed as Lennox-Gastaut syndrome. J Clin Neurophysiol 18:419–428
73. Mamelak AN, Barbaro NM, Walker JA, Laxer KD (1993) Corpus callosotomy a quantitative study of extent of resection, seizure control, and neuropsychological outcome. J Neurosurg 79:688–695
74. Marino Junior R (1985) Surgery for epilepsy. Selective partial microsurgical callosotomy for intractable multiform seizures: criteria for clinical selection and results. Appl Neurophysiol 48:404–407
75. Marlow BA, Edwards J, Marzec M, Sagher O, Ross D, Fromes G (2001) Vagus nerve stimulation reduces daytime sleepiness in epilepsy patients. Neurology 57:879–884
76. Maxwell RE, Gates JR, Gumnit RJ (1986) Corpus callosotomy at the University of Minnesota. In: Engel J Jr (ed) Surgical treatment of epilepsies. Raven Press, New York, pp 659–666
77. McLachlan RS (1993) Suppression of interictal spikes and seizures by stimulation of the vagus nerve. Epilepsia 94:918–923
78. Mirski MA, Ferrendelli JA (1986) Anterior thalamic mediation of generalized pentylenetetrazol seizures. Brain Res 399:212–223
79. Mirski MA, Rossell LA, Terry JB, Fisher RS (1997) Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res 28:89–100
80. Morrell F, Whisler WW, Smith MC, Hoeppner TJ, de Toledo-Morrell L, Pierre-Louis SJ, Kanner AM, Buelow JM, Ristanovic R, Bergen D et al (1995) Landau-Kleffner syndrome. Treatment with subpial intracortical transection. Brain 118:1529–1546
81. Morrell F, Whisler WW, Bleck TP (1989) Multiple subpial transection. A new approach to the surgical treatment of focal epilepsy. J Neurosurg 70:231–239
82. Morrell M, Hirsch L, Bergey G, Barkley G, Wharen R, Murro A, Fisch B, Rossi M, Labar D, Duckrow R, Sirven J, Drazkowski J, Worrell G, Gwinn R (2008) Long-term safety and efficacy of the RNS™ system in adults with medically intractable partial onset seizures. Epilepsia 49:480
83. Morris GL, Mueller MW (1999) Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The vagus nerve stimulation study group E01-E05. Neurology 53:1731–1735
84. Mountcastel VB (1997) The columnar organization of the neocortex. Brain 120:701–722
85. Mountcastle VB (1957) Modality and topographic properties of single neurons of cat's somatic cortex. J Neurophysiol 20:408–434
86. Mulligan LP, Spencer DD, Spencer SS (2001) Multiple subpial transections: the Yale experience. Epilepsia 42:226–229
87. Murphy JV, for the Pediatric VNS Study Group (1999) Left vagal nerve stimulation in children with medically refractory epilepsy. J Pediatr 134:563–566
88. Murphy JV, Torkelson R, Dowler I, Simon S, Hudson S (2003) Vagal nerve stimulation in refractory epilepsy: the first 100 patients receiving vagal nerve stimulation at a pediatric center. Arch Pediatr Adolesc Med 157:260–264
89. Narabayashi H, Nago T, Saito Y, Yoshida M, Nagahata M (1963) Stereotaxic amygdalotomy for behavior disorders. Arch Neurol 9:1–16
90. Nei M, O'Connor M, Liporace J, Sperling MR (2006) Refractory generalized seizures: response to corpus callosotomy and vagal nerve stimulation. Epilepsia 47:115–122
91. Orbach D, Romanelli P, Devinsky O, Doyle W (2001) Late seizure recurrence after multiple subpial transections. Epilepsia 42:1316–1319

92. Osorio I, Overman J, Giftakis J, Wilkinson SB (2007) High frequency thalamic stimulation for inoperable mesial temporal epilepsy. Epilepsia 48:1561–1571
93. Parrent AG, Lozano AM (2000) Stereotactic surgery for temporal lobe epilepsy. Can J Neurol Sci. 27 Suppl 1:S79-84; discussion S92–6. Review.
94. Patwardhan RV, Strong B, Bebin EM, Mathisen J, Grabb PA (2000) Efficacy of vagal nerve stimulation in children with medically refractory epilepsy. Neurosurgery 47:1353–1357; discussion 1357–1358
95. Penry JK, Dean JC (1990) Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results. Epilepsia 31(Suppl 2):S40–S43
96. Pinard JM, Delalande O, Chiron C, Soufflet C, Plouin P, Kim Y, Dulac O (1999) Callosotomy for epilepsy after West syndrome. Epilepsia 40:1727–1734
97. Polkey CE (2001) Multiple subpial transection: a clinical assessment. Int Rev Neurobiol 45:547–569
98. Purves SJ, Wada JA, Woodhurst WB (1995) Corpus callosum section for complex partial seizures. In: Reeves AG, Roberts DW (eds) Epilepsy and the corpus callosum 2. Advances in behavioral biology, vol 45. Plenum, New York, pp 175–182
99. Purves SJ, Wada JA, Woodhurst WB, Moyes PD, Strauss E, Kosaka B, Li D (1988) Results of anterior corpus callosum section in 24 patients with medically intractable seizures. Neurology 38:1194–1201
100. Rahimi SY, Park YD, Witcher MR, Lee KH, Marrufo M, Lee MR (2007) Corpus callosotomy for treatment of pediatric epilepsy in the modern era. Pediatr Neurosurg 43:202–208
101. Rathore C, Abraham M, Rao RM, George A, Sankara Sarma P, Radhakrishnan K (2007) Outcome after corpus callosotomy in children with injurious drop attacks and severe mental retardation. Brain Dev 29:577–585
102. Reeves AG, Risse G (1995) Neurological effects of callosotomy. In: Reeves AG, Roberts DW (eds) Epilepsy and the corpus callosum 2. Advances in behavioral biology, vol 45. Plenum, New York, pp 241–251
103. Reichenthal E, Hocherman S (1977) The critical cortical area for development of penicillin-induced epilepsy. Electroencephalogr Clin Neurophysiol 42:248–251
104. Renfroe JB, Wheless JW (2002) Earlier use of adjunctive nerve stimulation therapy for refractory epilepsy. Neurology 59:S26–S30
105. Rosenfeld WE, Roberts DW (2009) Tonic and atonic seizures: what's next – VNS or callosotomy? Epilepsia 50(suppl 8):25–30
106. Rougier A, Sundstorm L, Claverie B, Saint-Hilaire JM, Labrecque R, Lurton D, Bouvier G (1996) Multiple subpial transection: report of 7 cases. Epilepsy Res 24:57–63
107. Rutecki P (1990) Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation. Epilepsia 31(suppl 2):S1–S6
108. Sawhney IM, Robertson IJ, Polkey CE, Binnie CD, Elwes RD (1995) Multiple subpial transection: a review of 21 cases. J Neurol Neurosurg Psychiatry 58:344–349
109. Schachter SC (2002) Vagus nerve stimulation therapy summary: five years after FDA approval. Neurology 59(6 Suppl 4):S15–20. Review
110. Scherrmann J, Hoppe C, Kral T, Schramm J, Elger CE (2001) Vagus nerve stimulation: clinical experience in a large patient series. J Clin Neurophysiol 18:408–414
111. Schramm J, Aliashkevich AF, Grunwald T (2002) Multiple subpial transections: outcome and complications in 20 patients who did not undergo resection. J Neurosurg 97:39–47
112. Shahwan A, Bailey C, Maxiner W, Harvey AS (2009) Vagus nerve stimulation for refractory epilepsy in children: more to VNS than seizure frequency reduction. Epilepsia 50:1220–1228
113. Shimizu H (2005) Our experience with pediatric epilepsy surgery focusing on corpus callosotomy and hemispherectomy. Epilepsia 46(suppl 1):30–31
114. Shimizu H, Maehara T (2000) Neuronal disconnection for the surgical treatment of pediatric epilepsy. Epilepsia 41(Suppl 9):28–30
115. Smyth MD, Klein EE, Dodson WE, Mansur DB (2007) Radiosurgical posterior corpus callosotomy in a child with Lennox-Gastaut syndrome. J Neurosurg 106(4 Suppl):312–315

116. Smyth MD, Tubbs RS, Bebin EM, Grabb PA, Blount JP (2003) Complications of chronic of chronic vagus nerve stimulation for epilepsy in children. J Neurosurg 99:500–503
117. Spencer SS, Schramm J, Wyler A, O'Connor M, Orbach D, Krauss G, Sperling M, Devinsky O, Elger C, Lesser R, Mulligan L, Westerveld M (2002) Multiple subpial transection for intractable partial epilepsy: an international meta-analysis. Epilepsia 43:141–145
118. Sunaga S, Shimizu H, Sugano H (2009) Long-term follow-up of seizure outcomes after corpus callosotomy. Seizure 18:124–128
119. Tanriverdi T, Olivier A, Poulin N, Andermann F, Dubeau F (2009) Long-term seizure outcome after corpus callosotomy: a retrospective analysis of 95 patients. J Neurosurg 110:332–342
120. Tatum WOT, Helmers SL (2009) Vagus nerve stimulation and magnet use: optimizing benefits. Epilepsy Behav 15:299–302
121. Tellez-Zenteno JF, Dhar R, Wiebe S (2005) Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain 128:1188–1198
122. Tellez-Zenteno JF, McLachlan RS, Parrent A, Kubu CS, Wiebe S (2006) Hippocampal electrical stimulation in mesial temporal lobe epilepsy. Neurology 66:1490–1494
123. Turanli G, Yalnizoglu D, Genc-Acikgoz D, Akalan N, Topcu M (2006) Outcome and long-term follow-up after corpus callosotomy in childhood onset intractable epilepsy. Childs Nerv Syst 22:1322–1327
124. Uthman BM, Reichl AM, Dean JC, Eisenschenk S, Gilmore R, Reid S, Roper SN, Wilder BJ (2004) Effectiveness of vagus nerve stimulation in epilepsy patients: a 12-year observation. Neurology 63:1124–1126
125. Van Buren JM, Wood JH, Oakley J, Hambrecht F (1978) Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. J Neurosurg 48:407–416
126. Van Wagenen WP, Herren RY (1940) Surgical division of commisural pathways in the corpus callosum: relation to spread of an epileptic attack. Arch Neurol Psychiatry 44:740–759
127. Velasco AL, Velasco F, Jimenez F, Velasco M, Castro G, Carrillo-Ruiz JD, Fanghänel G, Boleaga B (2006) Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of qualitiy of life in patients with Lennox-Gastaut syndrome. Epilepsia 47:1203–1212
128. Velasco AL, Velasco M, Velasco F, Trejo D, Castro G, Carrillo-Ruiz JD (2007) Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. Epilepsia 48:1895–1903
129. Velasco F, Carrillo-Ruiz JD, Brito F, Velasco M, Velasco AL, Marquez I, Davis R (2005) Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. Epilepsia 46:1071–1081
130. Velasco F, Velasco M, Ogarrio C, Fanghanel G (1987) Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia 28:421–430
131. Vonck K, Thadani V, Gilbert K, Dedeurwaerdere S, De Groote L, De Herdt V, Goossens L, Gossiaux F, Achten E, Thiery E, Vingerhoets G, Van Roost D, Caemaert J, De Reuck J, Roberts D, Williamson P, Boon P (2004) Vagus nerve stimulation for refractory epilepsy: a transatlantic experience. J Clin Neurophysiol 21:283–289
132. Vonck K, Van LK, Dedeurwaerdere S, Caemaert J, De RJ, Boon P (2001) The mechanism of action of vagus nerve stimulation for refractory epilepsy: the current status. J Clin Neurophysiol 18:394–401
133. Wadman WJ, Gutnick MJ (1993) Non-uniform propagation of epileptiform discharge in brain slices of rat neocortex. Neuroscience 52:255–262
134. Wheless JW (2009) Managing severe epilepsy syndromes of early childhood. J Child Neurol 24:24S–32S
135. Wille C, Steinhoff BJ, Altenmüller DM, Staak AM, Bilic SB, Nikkhah G, Vesper J (2011) Chronic high-frequency deep-brain stimulation in progressive myoclonic epilepsy in adulthood – report of five cases. Epilepsia 52(3):489–496

136. Wilson DH, Culver C, Waddington M, Gazzaniga M (1975) Disconnection of the cerebral hemispheres. An alternative to hemispherectomy for the control of intractable seizures. Neurology 25:1149–1153
137. Wilson DH, Reeves A, Gazzaniga M, Culver C (1977) Cerebral commissurotomy for control of intractable seizures. Neurology 27:708–715
138. Wong TT, Kwan SY, Chang KP, Hsiu-Mei W, Yang TF, Chen YS, Yi-Yen L (2006) Corpus callosotomy in children. Childs Nerv Syst 22:999–1011
139. Wright GD, McLellan DL, Brice JG (1994) A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. J Neurol Neurosurg Psychiatry 47:769–774
140. Zachnetti A, Wang SC, Moruzzi G (1952) The effect of vagal afferent stimulation on the EEG pattern of the cat. Electroencephalogr Clin Neurophysiol 4:357–361
141. Zentner J (1997) Surgical aspects of corpus callosum section. In: Tuxhorn I, Holthausen H, Boenigk H (eds) Paediatric epilepsy syndromes and their surgical treatment. John Libbey, London, pp 830–849