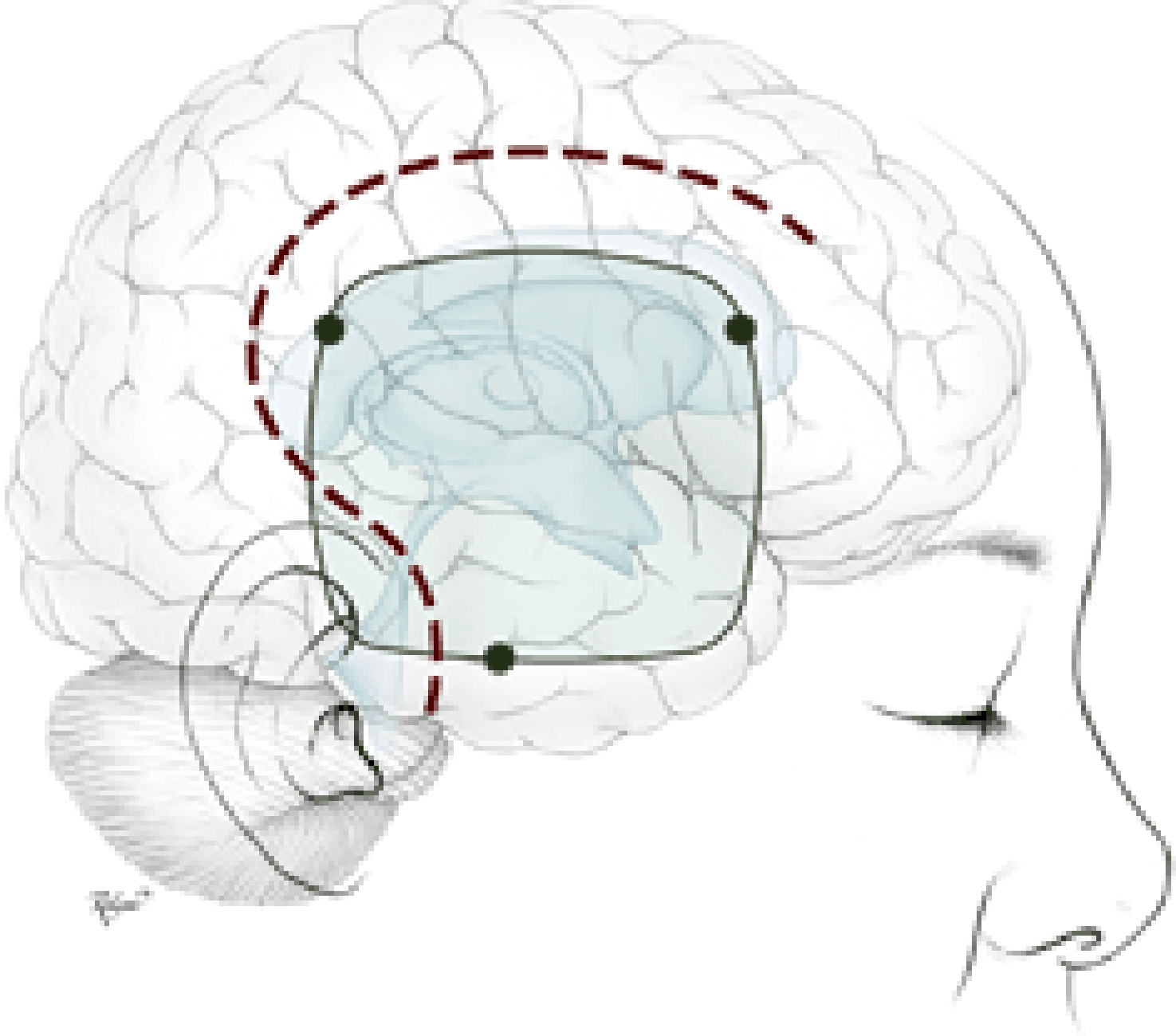

Introduction

Current concepts in epilepsy surgery

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Surgical treatment of medically intractable seizure disorders is a growing area in neurosurgery, a growth that has incorporated advances in neuroimaging, image-guided surgery, miniaturization of electronics, and development of brain-computer interfaces. This issue of *Neurosurgical Focus* presents 14 thoroughly researched and well-balanced articles that contain valuable new information for the epilepsy surgery team of neurosurgeons, intensivists, neurologists, neuroradiologists, neuropsychologists, nurses, and other staff who care for individuals with seizure disorders.

The articles in this issue of *Focus* are organized and presented in an order that takes the reader from demographic aspects of epilepsy to diagnostic methods, to aspects of resection, and then to neuromodulation. In the following sequence of authors and articles, the author cited is the corresponding author, and numbers refer to the order of the articles. This *Focus* issue contains a rich harvest of stimulating material.

Articles 1 and 2: the health care burden of patients with epilepsy is discussed by Vale, and inequities in access to pediatric epilepsy surgery by Bernstein.

Articles 3 and 4: new methods of diagnosis and prognosis are discussed by Fountas and Dulay.

Article 5: epilepsy as a manifestation of a specific disorder is discussed by Evans.

Articles 6 and 7: surgical techniques are discussed by Desai (recording from the insula) and by Rangel-Castilla (hemispherectomy).

Articles 8–10: analyses of resective surgery are given by Sagher (seizure outcomes and mesial resection volumes following temporal lobectomy), by Vale (failed surgery for mesial temporal sclerosis), and by Kershenovich (outcome of resection in posttraumatic epilepsy).

Articles 11–14: neuromodulation is discussed by Dlouhy (lead revision in vagal nerve stimulation), by Guthikonda (vagal nerve stimulation literature review), by Yoshor (brain stimulation), and by Chang (comparison of vagus nerve, thalamic deep brain stimulation, and responsive neurostimulation).

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Disclosure

Dr. Liu is a consultant for Integra, and Dr. Verma has served on the speakers bureau for Cyberonics.

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The health care burden of patients with epilepsy in the United States: an analysis of a nationwide database over 15 years

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Object. The aim of this study was to analyze the national health care burden of patients diagnosed with epilepsy in the US and to analyze any changes in the length of stay, mean charges, in-hospital deaths (mortality), and disposition at discharge.

Methods. A retrospective review of the Nationwide Inpatient Sample (NIS) database for epilepsy admissions was completed for the years from 1993 to 2008. The NIS is maintained by the Agency for Healthcare Research and Quality and represents a 20% random stratified sample of all discharges from nonfederal hospitals within the US. Patients with epilepsy were identified using ICD-9 codes beginning with 345.XX. Approximately 1.1 million hospital admissions were identified over a span of 15 years.

Results. Over this 15-year period (between 1993 and 2008), the average hospital charge per admission for patients with epilepsy has increased significantly ($p < 0.001$) from $10,050 to $23,909, an increase of 137.9%. This is in spite of a 33% decrease in average length of stay from 5.9 days to 3.9 days. There has been a decrease in the percentage of in-hospital deaths by 57.9% and an increase in discharge to outside medical institutions.

Conclusions. The total national charges associated with epilepsy in 2008 were in excess of $2.7 billion (US dollars, normalized). During the studied period, the cost per day for patients rose from $1703.39 to $6130.51. In spite of this drastic increase in health care cost to the patient, medical and surgical treatment for epilepsy has not changed significantly, and epilepsy remains a major source of morbidity.
(http://thejns.org/doi/abs/10.3171/2012.1.FOCUS11322)

Key Words • **epilepsy** • **socioeconomics** • **outcome** • **Nationwide Inpatient Sample**

It has been estimated that approximately 1% of the US population suffers from epilepsy.[9,11] Epilepsy is a unique disease to analyze from an economic standpoint. The high prevalence, high morbidity, and low mortality of this disease combine to create a disproportionately high cost of illness compared with other diseases.[5] Analysis of the disease is made difficult by the heterogeneous patient population; although 80% of patients diagnosed with epilepsy will achieve effective remission of the disease after approximately 5 years, a sizeable portion of patients will suffer from medically intractable epilepsy.[5] Recent years have seen different avenues of treatment emerge for such patients, such as new surgical techniques and VNS.[19,20] New developments in therapy for epilepsy coupled with advances in diagnostic technology have led to an increase in interventions. In spite of this, epilepsy remains a prevalent problem in the acute care setting worldwide.

Several international studies have addressed the epidemiology of health care in epilepsy; however, there are a limited number of papers that have addressed the socioeconomic changes in the care provided in the US.[8,15] In their review article, Strzelczyk et al.,[17] analyzed the cost of the illness of epilepsy, including indirect expenses to patients with epilepsy, by evaluating 22 studies worldwide. These authors also emphasized the need for studies that evaluate the impact that new antiepileptic treatments have had on the current cost of illness in epilepsy in the US. To our knowledge, there are no current studies that have analyzed trends in admissions, cost, and disposition of epilepsy in the US.

Abbreviations used in this paper: EEG = electroencephalography; LOS = length of stay; NIS = Nationwide Inpatient Sample; VNS = vagus nerve stimulation.

This retrospective study aims to analyze trends related to epilepsy in a nationwide database and to examine the health care burden of this disease. This analysis focuses on changes in LOS, mean hospital charge, in-hospital deaths, and disposition of the epileptic patient after hospitalization. By evaluating the data of more than 1.1 million patients admitted to the hospital for epilepsy in the US, we aim to bypass several limitations of international and private studies that include differing standards of care in practice, varying study populations, and heterogeneous economic climates that currently exist worldwide.

Methods

Clinical data were extracted from the NIS for the years 1993 through 2008. The NIS, which is maintained by the Agency for Healthcare Research and Quality, represents a 20% random stratified sample of all discharges from nonfederal hospitals within the US. It is the largest all-payer inpatient care database in the US and contains data from about 8 million hospital stays from 1000 hospitals each year. The NIS is the only national hospital database containing charge information for all patients, regardless of payer, including persons covered by Medicare, Medicaid, private insurance, and the uninsured. Patients with epilepsy diagnoses were identified using the corresponding ICD-9-CM codes (345.00–345.9) as a primary diagnosis code. Other seizure codes such as febrile seizure (780.31) were not included.

The Healthcare Cost and Utilization Project (HCUP) Internet tool (http://hcupnet.ahrq.gov/) was used to extract data on discharges, LOS, mean hospital charges, in-hospital deaths, and disposition of the epileptic patient after hospitalization (accessed October 15, 2010). When accessing the NIS data set through the HCUPnet tool, a weighted factor is already applied and national estimates are generated. A Bureau of Labor statistics tool (http://www.bls.gov/data/inflation_calculator.htm) was used to adjust hospital and national charges for inflation (normalized charges). Population-adjusted rates (discharges per measure of population) were calculated using population estimates generated by the US Census Bureau. The t-test (version 17.0, SPSS, Inc.) was used to determine statistical significance between data sets. A p value < 0.05 was considered significant.

Results

We identified approximately 1.1 million hospitalizations with epilepsy constituting the principal diagnosis (ICD-9-CM codes 345.XX). In this group, there were significant changes ($p < 0.001$) in all criteria evaluated, including the normalized number of discharges, LOS, normalized charges and national bill, in-hospital deaths, and patient disposition (Table 1).

Changes in Hospital Stay and Cost

The total number of patients with epilepsy seen in the acute health care setting, as measured by total number of discharges with ICD-9-CM coding 345 increased from 1993 (68,676 patients) to 2008 (170,484 patients), representing an increase of 107% (Table 2). The average LOS decreased from 5.9 days in 1993 to 3.9 days in 2008 (Fig. 1). However, adjusted hospital charges per hospitalization increased from $10,050 to $16,046 per admission, a relative increase of cost by 59.7% (Fig. 2). The national health care bill for acute care for epileptic patients in 1993 was just over $690,000,000, while the bill in 2008 soared to $2,735,586,000 (normalized charges).

Changes in Disposition After Hospital Stay

In-hospital mortality rates have decreased by 57.9% (Fig. 3). Disposition planning has also evolved over the past 15 years, with several changes in the plan of care for patients once discharged from the acute health care setting. Transfer discharges to other short-term hospitals decreased by 12.5% (Fig. 4). Meanwhile, there has been a

TABLE 1: Overall change from 1993 to 2008

Variable*	1993	2008	Δ (% change)	p Value†
mean total no. of discharges	68,676 ± 89	170,484 ± 414	148	
normalized discharges	0.27	0.56	107	
mean LOS in days	5.9 ± 0.6	3.9 ± 0.3	−33.9	<0.001
mean charges	$10,050 ± 158	$23,909 ± 367	137.9	<0.001
normalized charges	$10,050	$16,046	59.7	
no. of patients (%)				
in-hospital deaths	1,313 (1.9)	1,274 (0.8)	−57.9	<0.001
routine discharge	53,204 (77.5)	125,598 (73.7)	−4.9	<0.001
another short-term hospital	1,628 (2.4)	3,598 (2.1)	−12.5	<0.001
another institution	2,344 (3.4)	23,192 (13.6)	300	<0.001
home health care	3,320 (4.8)	12,021 (7.1)	47.9	<0.001
against medical advice	1,096 (1.6)	4,675 (2.7)	68.8	<0.001
missing discharge status	214 (0.3)	61 (0.04)	−86.7	<0.001

* Mean values are presented as ± SE. The pooled standard error was calculated from all the various codes.

† Continuous variables were compared using the 2-group t-test, and discharge status was compared using the chi-square test.

TABLE 2: Yearly change*

Variable	1993	1994	1995	1996	1997	1998	1999	2000
mean no. of discharges	68,676 ± 89	58,079 ± 93	51,565 ± 91	46,387 ± 70	48,864 ± 78	48,345 ± 97	51,902 ± 64	46,549 ± 63
normalized discharges	0.27	0.22	0.20	0.17	0.18	0.18	0.19	0.17
mean LOS in days	5.9 ± 0.06	5.7 ± 0.01†	5.2 ± 0.05†	4.7 ± 0.05†	4.7 ± 0.03	4.6 ± 0.05†	4.8 ± 0.04†	4.8 ± 0.05
mean charges	$10,050 ± 158	$10,862 ± 159†	$10,405 ± 152†	$10,244 ± 121†	$11,127 ± 109†	$12,465 ± 135†	$14,543 ± 141†	$16,684 ± 230†
normalized charges	$10,050	$10,590	$9,865	$9,434	$10,017	$11,050	$12,613	$14,000
no. of patients (%)								
in-hospital deaths	1,313 (1.9)	1,056 (1.8)	831 (1.6)†	831 (1.8)	686 (1.4)†	653 (1.4)	831 (1.6)†	750 (1.6)
routine discharge	53,204 (77.5)	44,282 (76.2)†	39,147 (75.9)	34,771 (75.0)†	38,115 (78.0)†	38,057 (78.7)†	41,462 (79.9)†	36,787 (79.0)†
another short-term hospital	1,628 (2.4)	1,346 (2.3)	1,183 (2.3)	1,168 (2.5)	1,086 (2.2)†	1,163 (2.4)	1,213 (2.3)	1,164 (2.5)
another institution	2,344 (3.4)	2,224 (3.8)†	2,621 (5.1)†	2,578 (5.6)†	6,065 (12.4)†	5,894 (12.2)	5,804 (11.2)†	5,399 (11.6)
home health care	3,320 (4.8)	3,447 (5.9)†	3,074 (6.0)	2,694 (5.8)	2,182 (4.5)†	1,873 (3.9)†	1,951 (3.8)	1,851 (4.0)
against medical advice	1,096 (1.6)	926 (1.6)	801 (1.6)	604 (1.3)†	655 (1.3)	653 (1.4)	587 (1.1)†	539 (1.2)
missing discharge status	214 (0.3)	80 (0.1)†	59 (0.1)	14 (0.03)†	75 (0.2)†	52 (0.1)†	54 (0.1)	58 (0.1)

	2001	2002	2003	2004	2005	2006	2007	2008
mean no. of discharges	51,066 ± 130	49,327 ± 143	54,320 ± 135	57,738 ± 111	70,567 ± 141	73,146 ± 186	136,300 ± 293	170,484 ± 414
normalized discharges	0.18	0.17	0.19	0.20	0.24	0.24	0.45	0.56
mean LOS in days	4.9 ± 0.07†	5.0 ± 0.08†	4.8 ± 0.09†	4.5 ± 0.04†	4.6 ± 0.04†	4.3 ± 0.05†	4.0 ± 0.02†	3.9 ± 0.03†
mean charges	17,570 ± 288†	21,805 ± 475†	24,210 ± 516†	20,963 ± 283†	25,058 ± 355†	23,551 ± 340†	23,155 ± 142†	23,909 ± 367†
normalized charges	14,335	17,514	19,012	16,035	18,540	16,880	16,137	16,046
no. of patients (%)	694 (1.4)†	735 (1.5)	728 (1.3)†	675 (1.2)	667 (1.0)†	695 (1.0)	799 (0.6)†	1,274 (0.8)†
in-hospital deaths	40,708 (79.7)†	38,462 (78.0)†	43,822 (80.7)†	45,752 (79.2)†	58,080 (82.3)†	57,652 (78.8)†	101,185 (74.2)†	125,598 (73.7)†
routine discharge	1,224 (2.4)	1,206 (2.5)	1,228 (2.3)	1,185 (2.1)	1,385 (2.0)	1,321 (1.8)†	3,018 (2.2)†	3,598 (2.1)
another short-term hospital	5,781 (11.3)	6,121 (12.4)†	5,603 (10.3)†	6,470 (11.2)†	6,038 (8.6)†	8,275 (11.3)†	19,051 (14.0)†	23,192 (13.6)†
another institution	1,944 (3.8)	2,095 (4.3)†	2,232 (4.1)	2,888 (5.0)†	3,507 (5.0)	3,992 (5.5)†	9,191 (6.7)†	12,021 (7.1)†
home health care	601 (1.2)	590 (1.2)	583 (1.1)	751 (1.3)†	857 (1.2)	1,185 (1.6)†	2,966 (2.2)†	4,675 (2.7)†
against medical advice	97 (0.2)†	112 (0.2)	91 (0.2)	—	—	12 (0.02)	54 (0.04)	61 (0.04)

* — = not available.

† $p \leq 0.01$.

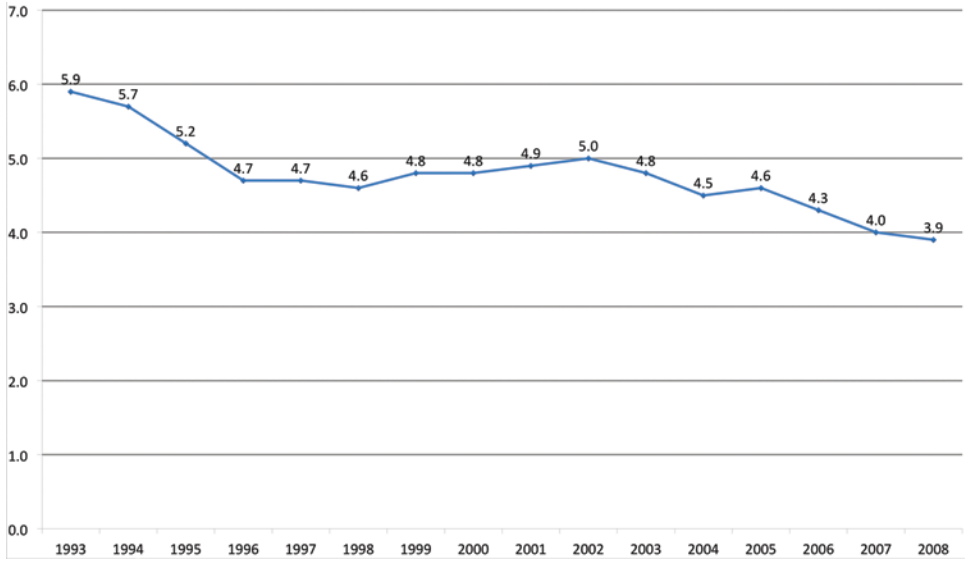

Fig. 1. Linear graph illustrates the average LOS per epilepsy admission (ICD-9-CM codes 345.XX) for the years 1993–2008.

net increase in discharge to other health care institutions of 300% (Fig. 5). Finally, there has been increased utilization of home health care, with an increase of 47.9% in home health services. These values are all summarized in Table 1.

Discussion

As the sensitivity of EEG and other diagnostic modalities that are used to recognize this disease increases, it is natural to assume that there will be a positive correlate in the number of admissions to acute care centers for seizure control.[2,4,12] This prediction has been substantiated in our recent analysis of admissions over the 15-year span studied, as evidenced by an increase in the number of patients discharged with epilepsy diagnoses. This increase has occurred despite the relative increases in the specificity of epileptic diagnostic modalities, and the advent of measures such as video-EEG monitoring and personality assessment inventories for ruling out confounding diagnoses, such as psychogenic seizures, that may have falsely increased the perceived health care burden of epilepsy.[13,21] Although the patient burden has increased dramatically, corresponding medical and surgical modalities of treatment have not yielded adequate results in decreased morbidity for patients, especially for epileptic patients who did not achieve disease control through surgical intervention.[14,16,18,19,22] The increase in prevalence described above has also been coupled with an overall increase in admission for epilepsy, as well as an increasing national health care bill as described by Bodenheimer.[6]

The results of our study highlight the continuous and significant health care burden of epilepsy in the US. The number of hospitalizations associated with a seizure disorder continues to increase with a concomitant increase in charges. Are the increases in these cases due to improved or more accurate diagnoses? Can the increase in cost result in better quality of life? The fact is that epilep-

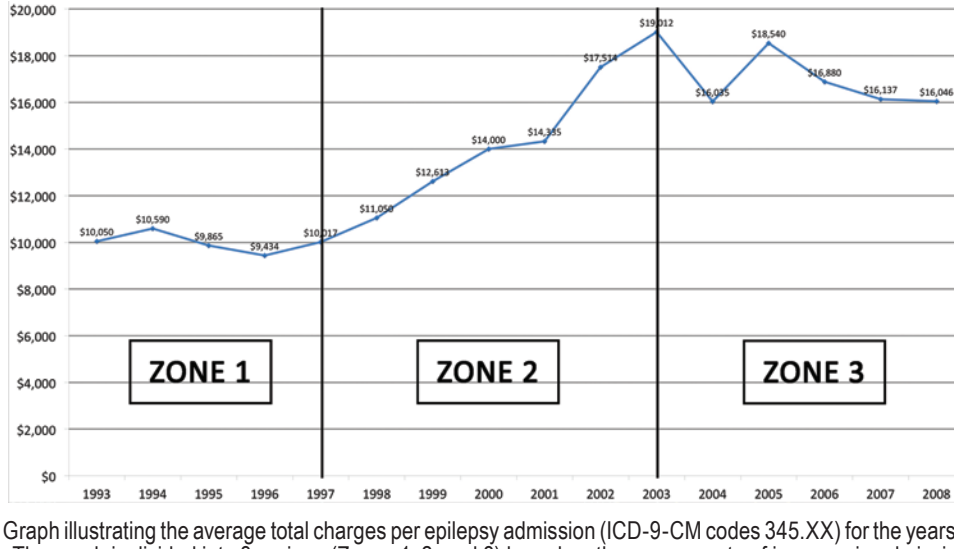

Fig. 2. Graph illustrating the average total charges per epilepsy admission (ICD-9-CM codes 345.XX) for the years 1993–2008 (adjusted). The graph is divided into 3 regions (Zones 1, 2, and 3) based on the average rate of increase in admission charges.

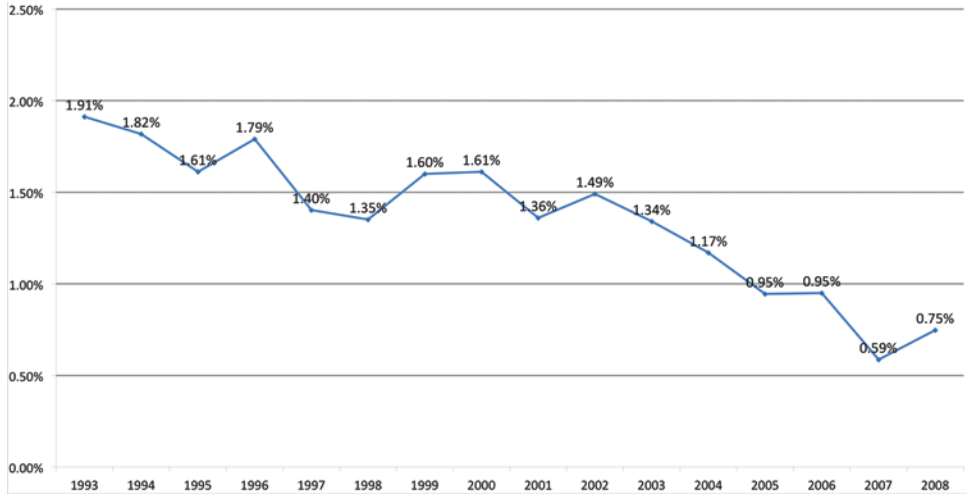

Fig. 3. Average in-hospital mortality (percentage of patients who were admitted for epilepsy and died) for admissions of patients with epilepsy (ICD-9-CM codes 345.XX) for the years 1993–2008.

sy has a heterogeneous presentation with varied treatment modalities. We may not be able to answer these questions, but the findings deserve special attention. First, we noted a dramatic and disproportionate increase in hospitalizations and charges associated with the care of patients with epilepsy. One hypothesis could be that because more epileptic patients are being identified in the emergency department, more are admitted for observation, follow-up imaging, or even surgical intervention, thus increasing costs. Second, we observed more transfers to other health care facilities. This finding may suggest an apparent lack of or limited improvement in status at discharge in this group of patients. Third, a significant decrease was observed regarding the LOS and in-hospital mortality rate. However, the need for increased home health care and skilled nursing facility utilization after discharge may suggest a disconnection between outcomes and the considerable progress in understanding epilepsy and the availability of new treatment options.

Advances in technology, access to video-EEG units, and improvement in the care of the critically ill patient might explain the increased costs of admission, the decreased mortality, and increased discharges to other institutions. In addition, the advent of VNS for treatment of medically and surgically intractable epilepsy was viewed as a turning point for patients upon its release in the late 1990s.[7] In our analysis of the average cost per admission for the epileptic patient, 3 areas of trend were noted. Figure 2 clearly illustrates periods of equivocal growth (in Zones 1 and 3), along with a 7-year period from 1997 to 2003 (Zone 2) with substantial growth. During the period of 1997–2003, the most significant addition to the treatment available for epileptic patients (either medical or surgical care) was the advent of VNS. The increased availability of VNS could potentially explain the augmented costs per admission as well as the decrease in LOS and increase in discharges to other institutions in some of these cases.[3] Nevertheless, VNS has opened the door to another set of

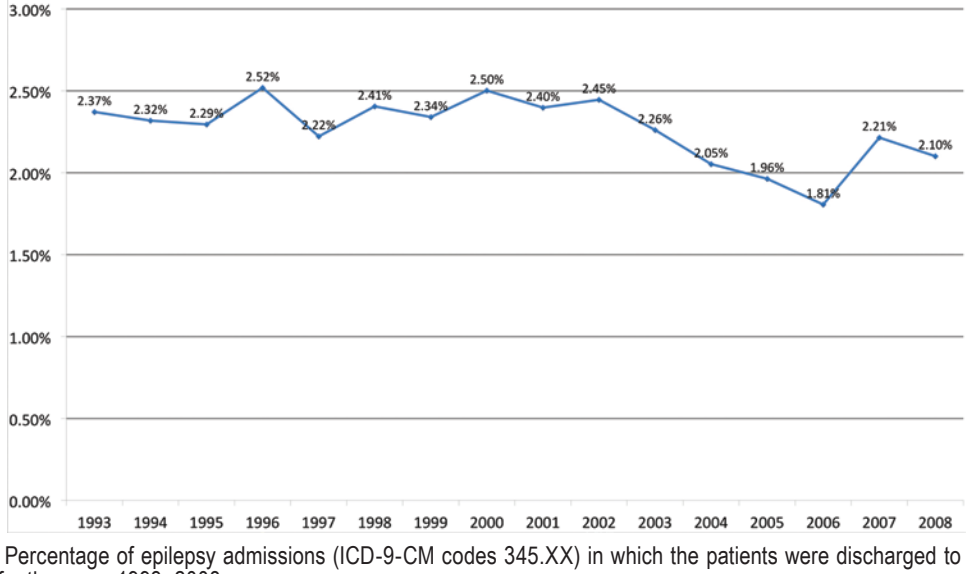

Fig. 4. Percentage of epilepsy admissions (ICD-9-CM codes 345.XX) in which the patients were discharged to short-term hospitals for the years 1993–2008.

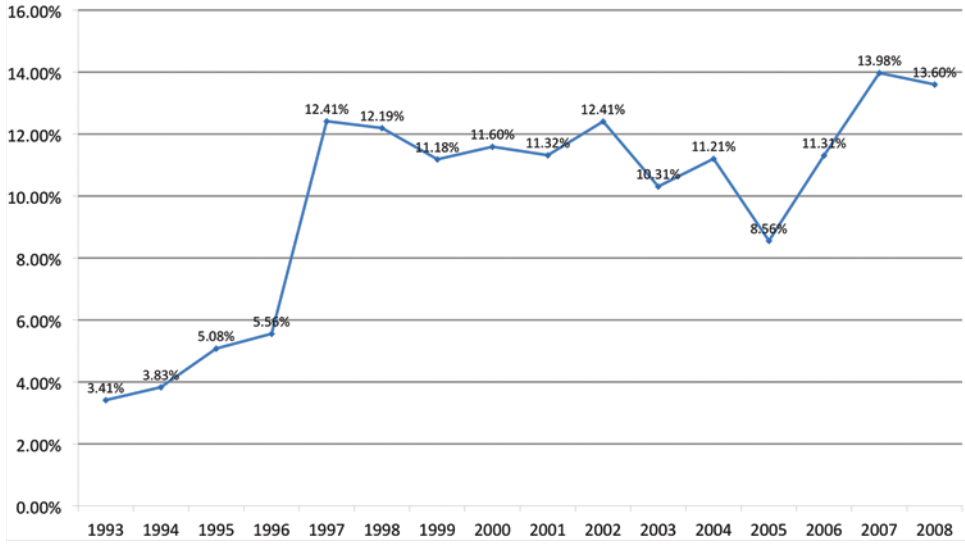

Fig. 5. Percentage of epilepsy admissions (ICD-9-CM codes 345.XX) in which the patients were discharged to other institutions (including facilities such as assisted-living facilities, rehabilitation centers, and skilled nursing facilities) for the years 1993–2008.

medically resistant epileptic patients with limited options for the treatment of their disease.

The NIS database has been widely used to analyze trends and outcome. Nonetheless, it represents only a 20% random, stratified sample of all patient discharges from nonfederal hospitals within the US. Although absolute conclusions are difficult to reach on the basis of these data, it is reasonable to analyze the relative trends over time. Our study has other limitations, and inaccurate coding of diagnoses and procedures could lead to over- or underestimates of the trends presented in the NIS database. In addition, limitations of the database do not allow for comparison (for example, emergency vs elective admissions) and assessment of "other" comorbidities that may impact the outcome and disposition in this patient population. This issue has been raised before.[1,3,10] When it comes to unique procedures, such as implantation of a VNS device, the coding is probably more accurate and consistent. Another limitation is that the data originate from a selected number of US hospitals, which may introduce bias in patient selection.

Conclusions

Trends from a national database reveal consistent increases in hospitalizations and charges for the evaluation and treatment of epileptic patients over a recent 15-year period. Despite increased charges, there were no significant improvements in immediate discharge status in this group during the period analyzed. Further studies are warranted to determine the cause of increased hospitalizations and ways to improve immediate discharge outcomes. The need to evaluate outcomes despite advances in technology cannot be overemphasized. It seems intuitive that a comprehensive evaluation of all forms of epilepsy is arguably best able to target appropriate patients for appropriate therapies.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Vale. Acquisition of data: Vivas, Baaj. Analysis and interpretation of data: Vivas, Baaj. Drafting the article: Vivas. Critically revising the article: Vale, Benbadis. Reviewed submitted version of manuscript: Vale. Approved the final version of the manuscript on behalf of all authors: Vale. Study supervision: Vale.

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Inequities in access to pediatric epilepsy surgery: a bioethical framework

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Epilepsy is a common childhood condition associated with a considerable medical and psychosocial burden. Children in whom medical treatment fails to reduce seizure burden represent an especially vulnerable patient population because prolonged, uncontrolled seizures are associated with poor developmental and neurocognitive outcomes. Surgical treatment in the form of cortical resection, functional disconnection, or neuromodulation may alleviate or significantly reduce the disease burden for a subset of these patients. However, there remains a dichotomy between the perceived benefits of surgery and the implementation of surgical strategies in the management of medically intractable epilepsy. The current paper presents an analysis of the bioethical implications of existing inequities in access to pediatric epilepsy surgery that result from inconsistent referral practices and discrepant evaluation techniques. The authors provide a basic bioethical framework composed of 5 primary expectations to inform public, institutional, and personal policies toward the provision of epilepsy surgery to afflicted children.
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Key Words • **ethics** • **pediatric epilepsy** • **epilepsy surgery**

Infants and children with prolonged, refractory epilepsy demonstrate worse cognitive outcomes, because seizures are thought to affect the developing brain adversely.[14,24] Longer duration of uncontrolled epilepsy is associated with a lesser likelihood of future freedom from seizures and worse developmental and behavioral outcomes.[1,7,8,17] It is well established that surgical treatment for resection of seizure foci, functional disconnection, or neuromodulation may bestow considerable benefit on afflicted children. Although a set of referral guidelines has been proposed for pediatric patients,[6] many children continue to face barriers in access to surgical interventions. In an international survey of pediatric epilepsy surgery centers, the mean duration of the disorder before surgery was 5.7 years, with significantly longer mean times for older children.[13] More importantly, this study also found that only a minority of children at greatest risk of epileptic encephalopathy received time-appropriate surgery. Particular patient populations at risk include children with refractory infant-onset epilepsies, in whom early surgical intervention has been shown to mitigate the detrimental effects of seizures on brain development.[16]

In the adult literature, a practice parameter established by the American Academy of Neurology in association with the American Epilepsy Society and the AANS recommended referral of adults with temporal lobe epilepsy to a surgical center after failure of first-line medication. In one study, the average adult referral time for presurgical evaluation from diagnosis was 18.6 years, with no statistically significant difference after the implementation of the practice guideline.[9] Because the majority of these patients are young adults, it is expected that a sizable subgroup may have benefited from surgical evaluation as children, and they are therefore germane to the subsequent discussion.

At present, it remains unclear why a dichotomy exists between the mounting evidence for early referral for surgical evaluation and the discordant lack of momentum in the implementation of surgical strategies for the management of medically intractable epilepsy in children. We discuss the implication of existing inequities in access to pediatric epilepsy surgery—as a result of inadequate referral patterns and discrepancies in presurgical evaluations—through an applied bioethical framework. The purpose is to identify ethical implications of inequities in access to surgery, and to inform public, institutional, and personal policies toward the provision of surgical treatments for childhood epilepsy.

Ethical Frameworks

Ethical frameworks function as scaffolding for shaping public health, institutional, and personal policies toward existing problems.[11] In the section of its influential 1983 report titled "An Ethical Framework for Access to Health Care," the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research made the distinction between health care and other commodities, where the former was deemed essential for quality of life and longevity.[27] The report identified ethical obligations for societies, institutions, and governments to facilitate equitable access to health-related resources. The distinction here between equality and equity in access to health care is paramount. The latter notion emphasizes the elimination of systemic disparities in access to health care between groups with different levels of underlying social advantages or disadvantages.[4] Whereas inequality is a reflection of social diversity, equity is a normative ethical value grounded in the principle of distributive justice.

Several frameworks exist for considering inequities in access to health care and/or limited resources. Wynia and Schwab[32] describe an ethical framework for the provision of health care coverage by defining 5 central expectations: 1) transparency; 2) participation; 3) equity and consistency; 4) sensitivity to value; and 5) compassion. In their review, Giacomini and colleagues[11] identified 17 themes that are common to a large number of policy-related ethical frameworks. To develop the current framework, we identified existing ethical challenges related to inequities in access to pediatric epilepsy surgery and classified them into 5 relevant expectations (Table 1).

Access. In the most basic sense, health care providers have an ethical obligation to facilitate access to epilepsy surgery for selected patient populations. This pertains to the physician's fiduciary duty—the obligation to "do good" enshrined in the Hippocratic oath, and comprises the first expectation of the current framework.[19] Intimately associated with this duty is the ability to identify children who would benefit from surgical intervention. In this sense, physicians have an obligation to appreciate the value of surgical intervention and to adhere to evidence-based guidelines. In fact, many conflicts between the roles of referring physicians as both patient advocates and gatekeepers of health care systems are mitigated by evidence-based outcomes and collaborative practice guidelines encouraging early referral patterns.[6]

Protection of the Vulnerable. Another expectation of the current framework is the protection of the vulnerable. Among children who face barriers in access to epilepsy surgery, there are various disproportionately affected subgroups. One such population is composed of children with nonlocalization-related epilepsies who may benefit from palliative procedures that could improve their quality of life by reducing seizure frequency. The implementation of palliative surgical strategies is however highly discrepant between centers.[13] Another subgroup comprises children with severe developmental delay. Epilepsy surgery pioneers Falconer[10] and Rasmussen[28] initially considered developmental delay to be a contraindication to epilepsy surgery; however, current practice guidelines do not discriminate against children with developmental delay, because this does not predict seizure outcome. Additionally, we have previously described ethical justifications for the consideration of palliative procedures for children with epilepsy as well as the role of surgical intervention in severely developmentally delayed children.[15] Other subgroups of children that have shown a lower rate of access to epilepsy surgery and antiepileptic medical therapy include African Americans, children whose parents have less education, older children, and those on polytherapy and with concurrent psychiatric diagnoses.[5] The identification and protection of these vulnerable subgroups of children is important to maintain beneficence and avoid maleficence when addressing inequities in access to epilepsy surgery.

Transparency. Many centers use different strategies for preoperative evaluation of children referred for surgi-

TABLE 1: A bioethical framework to address inequities in access to pediatric epilepsy surgery

Expectation	Duty
access	availability of surgical strategies for patients who may benefit
	adherence to evidence-based practices
	scrutiny of current practice limitations & pursuit of better diagnostic tools & treatments
protection of vulnerable patients	inclusion of children for consideration of palliative surgical procedures such as vagal nerve stimulation, corpus callosotomy, &/or hemispherectomy
	inclusion of children w/ developmental delay
	awareness & accommodation of marginalized populations
transparency	awareness of inter- & intrasurgeon variability in practices
	awareness of discrepancies in evaluation between different modalities
	surveillance of children for future surgical candidacy
	disclosure of evaluation methods & discrepancies during informed consent
equity despite inequality	application of best practices given current resources
	referral of complex cases to tertiary & quaternary centers
societal benefit	consideration of cost effectiveness of interventions

cal consideration, which has important implications on patient autonomy and informed consent. Whereas some discrepancies certainly arise from legitimate differences in opinion among centers, others may be partially due to discrepancies in localization technologies used and/or surgeon comfort. For example, centers continuing to use 1.5-T MRI units may miss lesions that are conspicuous on a 3-T scanner. Furthermore, the emergence of new technology to localize epilepsy creates an elusive standard of care that is difficult to define or implement.[12] The ultimate implication is that geographic location may affect a child's chances of surgical candidacy and freedom from seizures. Similar concerns have been raised for other conditions, including cancer, heart disease, and even the quality of prescribing practices.[23,29,33]

These regional differences in philosophies, practices, and technologies raise special considerations for informed consent and define the expectation of transparency within the current framework. One questions the extent to which clinicians have a responsibility to disclose discrepancies when obtaining informed consent. A valid argument would hold that to have full disclosure, one must include a discussion of differing localization technologies and approaches, with respective success rates. This may include disclosure of interinstitutional and intrainstitutional variation in success rates. Recently, there has also been increased focus on the publication of surgeons' performance, the so-called surgeon's report card,[25] as justified by numerous ethical arguments surrounding professional obligations and patient rights.[26] There are, however, challenges to such extensive disclosure, particularly in pediatric populations, because they typically have difficulty retaining information, so that full disclosure runs the risk of overwhelming patients and families.[18] Some authors also suggest that true full disclosure is altogether impossible due to unforeseen risk and clinician bias.[2]

Given the heterogeneity of practice and the wealth of emerging technologies, physicians also have an ethical obligation to monitor patients for the possibility of future surgical candidacy. In a study of 71 patients, most individuals who had once been rejected for epilepsy surgery (mainly due to the investigators' inability to localize the epileptogenic zone) were highly motivated to undergo new diagnostic procedures.[34] The challenge for clinicians therefore remains to: 1) recognize the limitations of their technology and approaches; 2) acknowledge their success and complication rates relative to others' practices; 3) apply the best technologies supported by the highest quality of evidence; and 4) perform ongoing surveillance of patients with intractable epilepsy for future surgical candidacy.

Equity Despite Inequality. As previously described, equity in health care is an ethical requirement for fair medical practices. The provision of equity despite inequality is a major challenge of health care systems. One study showed that uneven availability of resources, discrepant remuneration models, and plurality of provision of care all sustain inequity in access to elective surgical procedures.[22] Whereas some causes of inequity (such as poverty) are deep rooted and difficult to address, others, such as regional and urban-rural disparities in access to health care, can be overcome by simple measures such as the referral of complex cases to quaternary centers and centralization of specialized care.

Although the proposed bioethical framework is not intended to address global inequities in access, the inequity in access to pediatric epilepsy surgery in developing countries is also a significant consideration.[21] Eighty percent of the global burden of epilepsy lies in the developing world, and a staggering majority of patients receive ineffective management of their disease.[31] For afflicted children, the option of surgical intervention is often altogether unavailable. A thorough examination of the ethical challenges of epilepsy management in low-resource settings is beyond the scope of the current paper, but surgical strategies for the treatment of epilepsy in developing countries have been shown to be successful, sustainable, and ethically justifiable.[3,20]

Societal Benefit. The final expectation of the current framework is sensitivity to cost effectiveness. It has been demonstrated, for instance, that the application of surgical strategies for the treatment of refractory epilepsy is more cost effective than continued medical management.[30] In addressing inequities in access to pediatric epilepsy surgery, it is important to realize that these procedures may have an added societal benefit of reducing health care costs.

Conclusions

Children with medically intractable epilepsy comprise a vulnerable patient population facing numerous barriers in access to surgical interventions, which are imposed by inadequate referral patterns and discrepant evaluation techniques. We have identified the ethical implications of inaccessibility to surgical care and have proposed a bioethical framework for shaping public, institutional, and personal policies toward the provision of pediatric epilepsy surgery. We have identified 5 expectations to address existing inequities, as follows: 1) access (sensitivity to the value of surgical intervention); 2) protection of vulnerable populations; 3) transparency; 4) equity despite inequality; and 5) societal benefit. It is hoped that enhanced knowledge of the considerations presented in this framework will improve our ability to care for afflicted children.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Bernstein, Ibrahim, Barry, Fallah. Drafting the article: Ibrahim, Barry, Fallah. Critically revising the article: Bernstein, Ibrahim, Snead, Drake, Rutka. Study supervision: Bernstein, Snead, Drake, Rutka.

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Temporal pole proton preoperative magnetic resonance spectroscopy in patients undergoing surgery for mesial temporal sclerosis

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Object. The purpose of this prospective study was to compare the results of proton MR spectroscopy (MRS) in temporal poles in patients with unilateral mesial temporal sclerosis (MTS) with the histopathological findings of the resected temporal poles.

Methods. A total of 23 patients (14 male and 9 female) with a mean age of 25.2 years (range 17–45 years) were included in this study, which was conducted over a 4-year period. All patients suffered medically refractory epilepsy due to unilateral, MRI-proven MTS, with no other imaging abnormalities. All participants underwent preoperative single-voxel proton MRS using a 3-T MRI unit. The hippocampi and temporal poles were examined bilaterally. The concentrations of *N*-acetyl-aspartate (NAA), choline (Cho), and creatine (Cr) were measured, and the NAA/Cho, NAA/Cr, and NAA/Cho+Cr ratios were calculated. All patients underwent anterior temporal lobectomy and ipsilateral amygdalohippocampectomy, and surgical specimens from the temporal poles were sent for histopathological examination. Comparisons of the spectroscopic and histopathological results of the resected temporal poles were performed. The modified Engel classification system was used for evaluating seizure outcome in the cohort.

Results. The preoperative spectroscopic profiles of the sclerotic hippocampi were abnormal in all patients, and the contralateral hippocampus showed altered spectroscopic findings in 12 patients (52.2%). Spectroscopy of the temporal poles demonstrated severely decreased concentrations of NAA, markedly increased concentrations of Cho, and increased concentrations of Cr in the temporal pole ipsilateral to the MTS in 15 patients (65.2%). Similarly, the NAA/Cho, NAA/Cr, and NAA/Cho+Cr ratios were severely decreased in the temporal pole ipsilateral to the MTS in 16 patients (69.6%). Histopathological examination of the resected temporal poles demonstrated ischemic changes in 5 patients (21.7%), gliotic changes in 4 (17.4%), demyelinating changes in 3 (13.0%), and microdysplastic changes in 1 patient (4.3%). Comparisons of the spectroscopic and histopathological findings showed that the sensitivity of proton MRS was 100%, its specificity was 80%, its positive predictive value was 87%, and its negative predictive value was 100%. The mean follow-up time in this study was 3.4 years. At the end of the 2nd postoperative year, 17 patients (73.9%) were in Engel Class I, 5 (21.7%) were in Class II, and 1 (4.3%) was in Class III.

Conclusions. Proton MRS detected altered ipsilateral temporal pole metabolism in patients with unilateral MTS. These metabolic changes were associated with permanent histological abnormalities of the temporal pole. This finding demonstrates that MTS may be a more diffuse histological process, and exact preoperative knowledge of its temporal extent becomes of paramount importance in the selection of the best surgical approach in these patients. Further validation of the observations is necessary for defining the role of temporal pole proton MRS in cases of temporal lobe epilepsy.

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Key Words • epilepsy • gliosis • ischemia • mesial temporal sclerosis • magnetic resonance spectroscopy • temporal pole

It is widely accepted that MTLE constitutes the most common form of partial epilepsy in adults.[18,23] It has been estimated that approximately 20% of patients suffering from MTLE eventually develop medically refractory epilepsy.[6] Mesial temporal sclerosis represents one of the most common pathological entities responsible for MTLE.[19,24,26] The imaging and histopathological features of MTS regarding the hippocampus and the mesial temporal structures are well documented and have been extensively described in the literature. However, there is a growing body of evidence suggesting that MTS constitutes a more diffuse pathological entity, affecting

Abbreviations used in this paper: Cho = choline; Cr = creatine; EEG = electroencephalography; GABA = γ-aminobutyric acid; MRS = MR spectroscopy; MTLE = mesial temporal lobe epilepsy; MTS = mesial temporal sclerosis; NAA = *N*-acetyl-aspartate; TLE = temporal lobe epilepsy.

not only the mesial temporal lobe but also the temporal neocortex and even more distant cerebral areas, such as the frontal, parietal, and occipital lobes and the ipsilateral thalamus.[3,6,15,17–19,23,24,26]

Proton MRS is a noninvasive diagnostic tool that may provide valuable information regarding the biochemical profile and the metabolism of the brain. It has been extensively used in the preoperative evaluation of patients with medically intractable epilepsy, especially in cases of TLE, with varying specificity and accuracy rates.[2,4,5,8,11,13,20] The recent improvement of MR spectroscopic applications along with the accumulating experience with brain MRS have increased the use of proton MRS in the preoperative evaluation of patients with TLE. Proton MRS may detect even subtle changes in the concentration of the studied metabolites that may be implicated in seizure generation.[2,4,5,8,11,13,20]

The absolute concentrations of NAA, Cho, and Cr are usually measured, and their ratios NAA/Cho, NAA/Cr, NAA/Cho+Cr are calculated in the vast majority of temporal epilepsy cases.[2,4,5,8,11,13,20] Furthermore, the concentrations of inhibitory and excitatory neurotransmitters such as GABA and glutamate plus glutamine (GLX) have been used in a limited number of epilepsy cases of temporal origin.[24] There is a general consensus that proton MRS of the hippocampus in patients with MTS demonstrates decreased concentrations of NAA as a result of hippocampal gliosis and neuronal loss.[17,18] On the contrary, concentrations of Cho and Cr are increased, mainly due to the development of gliosis of the sclerotic hippocampus.[17,18]

In our current study, we present our findings from proton MRS of temporal poles in patients with MRI-proven unilateral MTS and medically refractory epilepsy. With this opportunity, we review the pertinent literature regarding the role of proton MRS in the extrahippocampal temporal lobe in patients with medically intractable epilepsy due to MTS.

Methods

Our prospective clinical study's protocol was approved by the institutional review boards of the participating institutions (University Hospital of Larissa and Institute "Euromedica-Encephalos"). All collected data were analyzed according to the Health Insurance Portability and Accountability Act regulations. A detailed written consent form was obtained from all participants or their legal guardians.

The study covered a 4-year period (January 2006 to December 2009). Our inclusion criteria included patients older than 16 years with medically intractable epilepsy (duration > 2 years while taking adequate doses of the appropriate anticonvulsant medications), unilateral MTS as noted on MRI, and clinically and electrographically proven seizures of temporal origin. Patients unable to undergo MRI or patients unable to cooperate for obtaining a proton MR spectroscopic study were excluded from the study.

A total of 26 patients met our inclusion criteria. However, 3 of these patients decided not to undergo surgery and were excluded from this study, leaving a population of 23 patients (14 male and 9 female). The mean age of our participants was 25.2 years (range 17–45 years), and the mean duration of epilepsy was 10.4 years (range 3–22 years). Detailed demographic data, as well as seizure-related and family histories, are summarized in Table 1.

All participants underwent preoperative evaluation including detailed clinical neurological examination, seizure semiology analysis, ictal and interictal surface video-EEG, brain MRI (special epilepsy protocol using a 3-T MRI unit for obtaining coronal oblique FLAIR and T1-weighted, high resolution T1-weighted, and 3D inversion recovery images), functional MRI study for language lateralization, and neuropsychological examination. Invasive EEG monitoring via depth and strip and/or grid subdural electrodes was necessary in 4 (17.4%) of the 23 patients.

Single-voxel proton MRS using a 3-T MRI unit (Signa HDxt, General Electric) was performed in all participants within 1 month prior to their resection. Bilateral hippocampi and both temporal poles were spectroscopically examined using a 1.5 × 1.5 × 1.5–cm voxel. The voxel

TABLE 1: Demographic and epilepsy-related history data of the participants*

Case No.	Age at Op (yrs), Sex	Duration of Epilepsy (yrs)	Hx of Febrile Szs	Other Predisposing Factors	Family Hx of Epilepsy
1	26, M	12	no	no	no
2	20, M	7	no	no	no
3	31, F	9	no	no	no
4	19, M	5	no	no	no
5	24, F	11	yes	meningitis	no
6	28, F	12	yes	no	no
7	30, M	14	no	no	no
8	22, M	18	yes	neonatal meningitis	no
9	19, M	4	no	no	no
10	28, F	7	yes	no	no
11	45, M	22	yes	no	no
12	21, F	11	no	no	no
13	20, F	5	no	no	no
14	35, M	16	no	no	no
15	23, M	8	yes	no	yes (father w/ epilepsy)
16	17, F	3	no	no	no
17	18, M	9	yes	no	no
18	26, M	10	no		no
19	20, F	3	yes	no	yes (mother w/ epilepsy)
20	33, F	24	no	no	no
21	27, M	16	no	no	no
22	19, M	3	no	no	no
23	29, M	11	no	no	no

* Hx = history; Szs = seizures.

placement was manual, and visual inspection ensured that the voxel contained only the temporal lobe without contamination from the surrounding tissues. Point-resolved spectroscopy (PRESS) was used with the following parameters: TE 35 msec, TR 1500 msec, and number of excitations 8. The average spectroscopic study duration for each temporal pole was approximately 5 minutes. The actual concentrations of NAA, Cho, and Cr, as well as the metabolic ratios NAA/Cr, NAA/Cho, and NAA/Cho+Cr, were calculated (Fig. 1).

All participants underwent anterior temporal lobectomy and ipsilateral amygdalohippocampectomy. A standard subpial aspiration/resection technique was routinely used in all cases. General endotracheal anesthesia was induced in 17 patients (73.9%), and awake craniotomy for language cortical mapping was used in the remaining 6 (26.1%). Postresection intraoperative corticography was used in all patients. Surgical specimens from the resected neocortex, as well as from the amygdala and the hippocampus, were sent for histopathological and immunohistochemical analyses in all cases.

The surgical outcome was evaluated using the modified Engel scale.[9] The mean follow-up time was 3.4 years (range 2–5 years).

Results

There were 15 patients with right-sided and 8 patients with left-sided MTS on the preoperatively obtained MRI studies (Table 2). The existence of hippocampal pathology was histologically confirmed in all cases in our series. Histopathological examination of the resected hippocampi revealed gliosis in 21 patients (91.3%), and ischemic changes were detected in 16 (69.6%).

Findings of proton MRS of the sclerotic hippocampi were abnormal in all cases. There was a significant decrease in the concentration of NAA on the sclerotic side compared with the contralateral hippocampus. It has to be mentioned, however, that in 12 patients (52.2%) even the theoretically normal hippocampus showed lower concentrations of NAA than sex- and age-matched controls from a historical healthy control group. Increased concentrations of Cho were found in the sclerotic hippocampus in 22 patients (95.7%) compared with the contralateral side, and increased Cr concentrations were measured in the affected hippocampus in 21 patients (91.3%). The NAA/Cho ratio of the sclerotic hippocampus was decreased in all patients, as were the NAA/Cr and NAA/Cho+Cr ratios.

Analysis of the proton MRS data obtained from the temporal poles demonstrated that there was a significant decrease in the NAA concentration on the same side as the MTS in 15 patients (65.2%). Similarly, increased concentrations of Cho and Cr were found in the temporal pole on the same side as the MTS in 13 patients (56.5%). The NAA/Cho ratio was decreased in the temporal pole on the same side as the MTS in 15 patients (65.2%), the NAA/Cr was decreased in 15 patients (65.2%), and the NAA/Cho+Cr ratio was decreased in 16 patients (69.6%). On the contrary, the spectroscopic analysis of the temporal pole contralateral to the MTS revealed no abnormalities in any of our study participants.

Comparisons of the sclerotic hippocampal and ipsilateral temporal pole spectroscopic findings showed significantly lowered NAA concentrations and markedly higher concentrations of Cho and Cr in the hippocampus. However, these differences were very subtle on the side contralateral to the MTS in 12 patients (52.2%), with slightly decreased NAA and mildly elevated Cho and Cr concentrations in the nonsclerotic hippocampus compared with the ipsilateral temporal pole, which showed a normal spectroscopic profile. In the remaining 11 patients (47.8%) the spectroscopic profiles of the nonsclerotic hippocampi and the contralateral to the MTS temporal poles were within normal limits.

Histopathological analysis of the resected temporal poles revealed that in 13 patients (56.5%) there was evidence of abnormality in the resected specimen. More

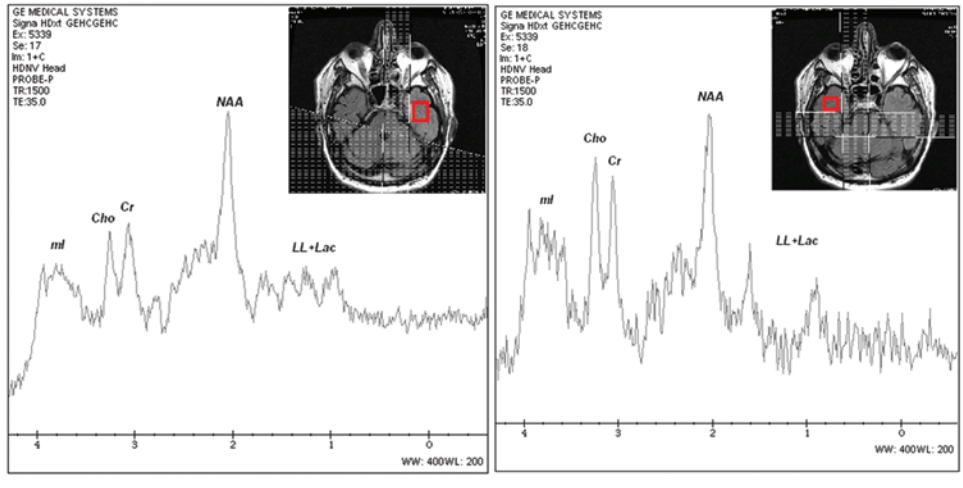

Fig. 1. Left: Single-voxel MRS performed in the left temporal pole (contralateral to the MTS) showing normal concentrations of NAA, Cho, and Cr. **Right:** Single-voxel MRS performed in the right temporal pole (ipsilateral to the MTS) showing an increased concentration of Cho and a slightly increased concentration of Cr, and a decreased concentration of NAA compared with the contralateral hemisphere.

TABLE 2: Synopsis of preoperative evaluation data and postoperative outcome in our cohort

Case No.	Side of MTS	Proton MRS Data				Invasive EEG Monitoring	Resected Hippocampus Histopathology	Resected Temporal Pole Histopathology	Engel Class at 2 Yrs
		Preop Sclerotic Hippocampus	Preop Nonsclerotic Hippocampus	Preop Ipsilat to MTS Temporal Pole	Preop Contralat to MTS Temporal Pole				
1	lt	abnormal	normal	abnormal	normal	yes	abnormal	abnormal	I
2	rt	abnormal	abnormal	abnormal	normal	no	abnormal	abnormal	II
3	rt	abnormal	normal	abnormal	normal	no	abnormal	normal	I
4	rt	abnormal	normal	normal	normal	no	abnormal	normal	II
5	lt	abnormal	normal	abnormal	normal	no	abnormal	abnormal	I
6	rt	abnormal	normal	abnormal	normal	no	abnormal	abnormal	I
7	rt	abnormal	normal	normal	normal	no	abnormal	normal	I
8	lt	abnormal	abnormal	normal	normal	yes	abnormal	normal	I
9	rt	abnormal	normal	abnormal	normal	no	abnormal	abnormal	I
10	rt	abnormal	normal	normal	normal	no	abnormal	normal	I
11	lt	abnormal	abnormal	abnormal	normal	no	abnormal	abnormal	I
12	lt	abnormal	normal	normal	normal	no	abnormal	normal	II
13	rt	abnormal	normal	abnormal	normal	no	abnormal	abnormal	II
14	rt	abnormal	abnormal	normal	normal	no	abnormal	normal	I
15	rt	abnormal	normal	abnormal	normal	no	abnormal	abnormal	I
16	lt	abnormal	normal	abnormal	normal	yes	abnormal	abnormal	I
17	rt	abnormal	abnormal	normal	normal	no	abnormal	normal	I
18	rt	abnormal	normal	abnormal	normal	no	abnormal	abnormal	II
19	rt	abnormal	abnormal	normal	normal	no	abnormal	normal	I
20	lt	abnormal	normal	abnormal	normal	no	abnormal	normal	III
21	rt	abnormal	normal	abnormal	normal	no	abnormal	abnormal	I
22	rt	abnormal	abnormal	abnormal	normal	no	abnormal	abnormal	I
23	lt	abnormal	abnormal	abnormal	normal	yes	abnormal	abnormal	I

specifically, ischemic changes were found in 5 patients (21.7%), gliosis was evident in 4 (17.4%), demyelination was found in 3 (13.0%), and microdysplastic changes were found in 1 patient (4.3%).

Comparative analysis of the temporal pole proton MRS and the neocortical temporal histopathological data shows that proton MRS detected the presence of metabolic abnormalities in the temporal neocortex ipsilateral to the MTS in 15 patients (65.2%). Interestingly, these metabolic changes were confirmed by the presence of pathological changes in 13 patients (56.5%). It has to be emphasized that none of the patients with normal temporal pole spectroscopic profiles had any neocortical histopathological abnormalities. In this series, the sensitivity of temporal pole proton MRS was 100%, its specificity was 80%, its positive predictive value was 87%, and its negative predictive value was 100%.

The use of postresection intraoperative corticography revealed no abnormalities on EEG in any of our cases, and therefore it played no role in modifying our initial resection plan. The observed seizure outcome at the 1st postoperative year was Class I in 18 patients (78.3%), Class II in 4 patients (17.4%), and Class III in 1 patient (4.3%). At the completion of the 2nd postoperative year, 17 patients (73.9%) were in Class I, 5 (21.7%) were in Class II, and 1 patient (4.3%) was in Class III. The relationship, if any, of temporal pole spectroscopic abnormalities with the surgical outcome cannot be established, since the population of our current study is very limited and any statistical analysis is essentially meaningless.

Discussion

Proton MRS has been extensively used in the evaluation of cerebral metabolism in epileptic patients and particularly in cases of MTS.[2,4,5,8,11,13,20] Several clinical series have documented that in patients with MTS there is a significant decrease in the concentration of NAA and increases in the concentrations of Cho and Cr in the affected hippocampus. Several clinical investigators have demonstrated with the aid of proton MRS that in cases of MTS, the ipsilateral extrahippocampal temporal lobe may have altered metabolism.[6,17–19,23,24,26] Meiners et al.[17] reported their experience with a series of 11 patients with hippocampal sclerosis who underwent single-voxel extrahippocampal temporal lobe proton MRS (Table 3). They found that the white matter of the temporal lobe ipsilateral to the hippocampal sclerosis demonstrated decreased concentrations of NAA, marked increase in Cho concentrations, a slight increase in Cr concentrations, and decreased NAA/Cho and NAA/Cr ratios.[17] Their findings are in agreement with our current study results. However,

TABLE 3: Synoptic presentation of the most important clinical series regarding extrahippocampal temporal lobe proton MRS in patients with MTS*

Authors & Year	Type of Study	No. of Patients/ No. of Controls	MRI Field Strength (T)	MRS Findings in Extrahippocampal Temporal Lobe
Meiners et al., 2000	prospective	11/12	1.5	NAA ↓↓, Cho ↑↑, Cr ↑, NAA/Cho ↓↓, NAA/Cr ↓
Capizzano et al., 2002	case-control horizontal	15/12	1.5	NAA/Cho + Cr ↓↓
Vermathen et al., 2003	prospective	11/13	1.5	NAA ↓↓, NAA/Cho + Cr ↓↓
Mueller et al., 2004	prospective	14/12	1.5	NAA/Cho + Cr ↓↓
Simister et al., 2009	prospective	16/15	1.5	NAA ↓↓, Cr ↑, NAA/Cr ↓↓, GABA unchanged
Mueller et al., 2011	prospective	25/0	4	NAA/Cho + Cr ↓↓
Shih et al., 2011	prospective	8/0	1.5	NAA/Cho ↓↓
current study	prospective	23/0	3	NAA ↓↓, Cho ↑↑, Cr ↑, NAA/Cho ↓↓, NAA/Cr ↓, NAA/Cho + Cr ↓↓

* ↑ = mild increase in concentration; ↑↑ = moderate to severe increase in concentration; ↓ = mild decrease in concentration; ↓↓ = moderate to severe decrease in concentration.

the histological examination of the temporal lobe white matter in their series showed no abnormalities.[17] Similarly, Shih et al.[23] reported their results from a series of 8 patients with MTS who underwent proton MRS of the lateral temporal lobe. These authors found that the NAA concentration was lower in the lateral temporal lobe on the same side as the MTS in 50% of their cases, while the concentration of Cho was increased in these patients. Moreover, these spectroscopic changes were accompanied by magnetoencephalographic changes originating from the same temporal neocortical areas. Capizzano et al.[6] reported similar temporal extrahippocampal spectroscopic findings from a series of 15 patients with MTS. These authors found severely decreased NAA concentrations in the temporal lobe ipsilateral to the MTS. Their findings are in agreement with the results of our study.

Likewise, Mueller et al.[18,19] reported their experience with spectroscopic imaging of patients suffering TLE. They found that MTS is associated with extrahippocampal reduction of NAA concentration, increased Cho and Cr concentrations, and a decreased NAA/Cho+Cr ratio. Their findings are in agreement with our current observations. They also postulated that these MTS-associated NAA, Cho, and Cr changes may not be limited to the ipsilateral temporal lobe but may extend and affect the ipsilateral frontal and parietal lobes. Vermathen et al.[26] reported their results from using extrahippocampal temporal lobe proton MRS in 11 patients with MTS. They found decreased concentrations of NAA and increased concentrations of Cho and Cr on the ipsilateral to the MTS temporal lobe. Their findings are in agreement with our results. They also claimed that NAA, Cho, and Cr changes were detectable not only in the ipsilateral temporal lobe but also in the entire ipsilateral hemisphere. Simister et al.[24] used proton MRS in 35 patients with MTS. They found that the temporal lobe affected by MTS showed decreased concentrations of NAA and increased concentrations of Cr, while the concentrations of GABA and glutamate/glutamine were essentially unchanged.[24]

The pathophysiological mechanism or mechanisms responsible for these extrahippocampal spectroscopic changes remain highly controversial. It has been postulated by Meiners et al.[17] that neuronal axonal loss may be responsible for the observed extrahippocampal NAA decrease. This loss of neuronal axons may explain the increased concentrations of Cho, since demyelination has been associated with increased Cho production. It is widely accepted that the obtained spectra from neonatal brains demonstrated increased Cho peaks, due to the incomplete myelination process.[25] However, Meiners et al. found no histological abnormalities in their temporal extrahippocampal specimens to support such demyelination process. Another proposed theory suggests that the spectroscopic extrahippocampal changes may be the result of extrahippocampal neuronal dysfunction caused by deafferentation due to loss of input from the hippocampal focus.[18] This may explain the observed extrahippocampal spectroscopic changes, which are accompanied by no or very subtle structural changes in these areas.[18] On the contrary, in our current series the well-documented temporal pole spectroscopic changes were associated with permanent structural changes of the temporal neocortex and white matter on the side affected by MTS. This may be another explanatory mechanism for the observed extrahippocampal metabolic changes in cases of MTS. Other investigators have suggested that MTS may be a more widespread pathological process than a focal structural abnormality.[23] If these structural and histopathological changes observed in our series are induced by the excitotoxic effect of hippocampal sclerosis and mesially originated seizure propagation, or constitute part of a widespread pathological process that involves both the hippocampus and the adjacent ipsilateral temporal lobe, remains to be defined. There is, however, a growing body of evidence that the extrahippocampal spectroscopic changes represent actual metabolic changes, since their presence has been demonstrated not only by proton MRS but also by PET and magnetoencephalography studies.[1,14,21,23]

Our proposed theory that extrahippocampal temporal spectroscopic measurements represent permanent structural and histological abnormalities is not supported by the observations of some clinical investigators.[7,12,22,24] Others have demonstrated that this abnormal extrahippocampal spectroscopic profile returns to normal after resection of the sclerotic hippocampus.[7,12,22,24] It has to be

emphasized, however, that this postoperative normalization of spectroscopic profile regards, in the vast majority of the reported cases, the contralateral hippocampus and not the ipsilateral extrahippocampal temporal lobe.[7,12,22,24] It may be postulated that some of the spectroscopically detected metabolic changes may well be a temporary result of tissue dysfunction, while some other changes, particularly of the adjacent ipsilateral temporal lobe, may be indicative of permanent structural changes. Further comparative studies between extrahippocampal temporal lobe spectroscopy and histopathological examination are necessary for clarifying this highly controversial issue.

Complete understanding of the underlying pathophysiological mechanism is of paramount importance not only for clarifying the MTS pathological process but also for selecting the most efficient surgical approach for these patients. If the spectroscopic changes represent permanent structural changes in the temporal neocortical and white matter on the side of the MTS, resection of these areas may increase the possibility of achieving better seizure outcome postoperatively. If the observed histopathological changes of the involved extrahippocampal temporal lobe in our series had not been resected, the postoperative seizure outcome could have been worse, since ischemic and/or gliotic foci would have remained intact to continue their potential epileptogenic activity. It could be postulated that the findings of proton MRS in the temporal pole could influence the decision for a selective amygdalohippocampectomy or a more extensive anterior temporal lobectomy and amygdalohippocampectomy.

It has to be emphasized that proton MRS constitutes a highly susceptible methodology to artifacts and intrinsic errors. Voxel contamination by the surrounding tissues may significantly alter the obtained spectrum and may lead to erroneous interpretations. The importance of signal contamination from a misplaced voxel has been adequately addressed in the literature.[10] In our current study, the voxel placement was manual and this was done with extreme caution by experienced spectroscopists. In addition, the proximity of bone and muscle tissue to the temporal fossa may influence the accuracy of the obtained spectra in rare instances.[24] It is well known that temporal lobe is a nonhomogeneous structure, and this may alter the accuracy of the obtained spectrum.[24] Moreover, it is known that gray and white matter have different spectroscopic profiles, thus making the interpretation of the obtained spectra quite puzzling.[16,24] In addition to the technical pitfalls of proton MRS, the limited number of cases included in our current study represents another limitation and decreases the strength of our study. The drawing of any conclusions regarding the role of any predisposing factors in developing diffuse temporal neocortex metabolic and histopathological changes is impossible due to the limited number of cases in our study. However, the number of participants in the vast majority of the published series is limited, since cases of unilateral MTS with no other pathology are relatively rare.[6,17,19,23,24,26] These limitations and technical weaknesses need to be taken into consideration in the clinical interpretation of our findings.

Conclusions

Proton MRS is a noninvasive imaging modality that provides valuable information regarding the metabolism not only of the hippocampi but also of the extrahipppocampal temporal lobes in patients with MTS. In our current study, proton MRS of the temporal poles in patients with unilateral, clearly defined MTS revealed severely decreased concentrations of NAA, markedly increased concentrations of Cho, increased concentrations of Cr, and severely decreased ratios of NAA/Cho+Cr in the temporal pole ipsilateral to the MTS. The histopathological examination of the resected temporal poles demonstrated ischemic, gliotic, demyelinating, and dysplastic changes, which may be associated with our spectroscopic findings. The role of proton MRS in the preoperative evaluation of patients with MTS, and especially in selecting the most appropriate surgical strategy (anterior temporal lobectomy plus amygdalohippocampectomy vs selective amygdalohippocampectomy), remains to be defined, since the permanent nature of the observed spectroscopic changes and their association with pathological entities requires further validation. Minimization of the technical pitfalls of proton MRS and larger clinical series may enlighten us on the pathophysiology of these spectroscopic changes and their role in the preoperative evaluation of patients suffering medically intractable epilepsy due to MTS.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Fountas, Kapsalaki. Acquisition of data: Fountas, Tsougos, Gotsis, Kapsalaki. Analysis and interpretation of data: Fountas, Tsougos, Gotsis, Kapsalaki. Drafting the article: Fountas. Critically revising the article: Fountas, Smith, Kapsalaki. Reviewed submitted version of manuscript: Giannakodimos. Approved the final version of the manuscript on behalf of all authors: Fountas. Administrative/technical/material support: Kapsalaki. Study supervision: Kapsalaki.

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Prediction of neuropsychological outcome after resection of temporal and extratemporal seizure foci

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Resection of seizure foci is an effective treatment for the control of medically intractable epilepsy. However, cognitive morbidity can occur as a result of surgical intervention. This morbidity is dependent on several factors, including location and extent of resection, disease characteristics, patient demographic characteristics, and functional status of the tissue to be resected. In this review article, the authors provide a summary of the neurocognitive outcomes of epilepsy surgery with an emphasis on presurgical predictors of postsurgical cognitive decline.
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Key Words • **neuropsychology** • **memory** • **postsurgical outcome** • **epilepsy**

Epilepsy affects approximately 1% of the US population. Thirty percent of patients who present to epilepsy specialty centers are diagnosed with intractable epilepsy and undergo a comprehensive evaluation for possible surgical intervention for seizure control. A diagnostic workup for surgical intervention includes medical and psychiatric history, neurological examination, video-electroencephalographic monitoring, structural MRI and other neuroradiological techniques, and neuropsychological testing. Neuropsychological assessment helps to identify patients at risk for cognitive decline following epilepsy surgery.

Resection of seizure foci is an effective treatment for medically intractable epilepsy. Of individuals who undergo unilateral ATR, the most common form of surgery for intractable epilepsy, between 66% and 70% achieve seizure freedom.[59] Of patients with seizures originating from the frontal lobe, approximately 57% are seizure free 1 year after surgery and 30% 5 years after surgery.[32] Resection not only has the potential to cure intractable epilepsy, but also can significantly improve health-related quality of life[57] and independence in activities of daily living,[35] increase the likelihood of return to work,[17] and improve cognitive functioning.[58] Problematically, in a subset of patients, resection can contribute to postoperative neurocognitive impairment and emotional disturbance.[44,58] In this review article, we provide a summary of the neurocognitive outcome of epilepsy surgery with an emphasis on presurgical predictors of postsurgical cognitive decline.

Abbreviations used in this paper: ATR = anterior temporal lobe resection; fMRI = functional MRI.

Memory After Left ATR

Verbal memory decline is the most consistently found impairment after left ATR.[25] Sections of the hippocampus and parahippocampal gyrus, removed as part of a standard ATR, are important for encoding and retrieval of verbal information for recent events. Between 22% and 63% of individuals who undergo left ATR experience a significant decline in verbal memory, while about 7% show improvement.[58] In contrast, between 10% and 34% of patients show improvement in verbal memory after right ATR.[58] The primary predictor of postsurgical verbal memory loss following left ATR is the presurgical functional status of the tissue to be resected. Functional integrity of the mesial temporal lobe can be estimated in a number of ways, including greater left medial temporal lobe activation during presurgical fMRI,[6] the absence of structural MRI abnormalities such as mesial temporal sclerosis,[63] a lack of significant asymmetry in temporal lobe activation on FDG-PET,[22] and intact presurgical verbal memory ability on neuropsychological[9] or Wada testing.[3] Later age at seizure onset is also associated with greater risk for memory decline following ATR, because individuals who have seizures that began in adulthood have a greater likelihood of developing adequate verbal memory abilities prior to the onset of seizures.[54]

Postsurgical verbal memory loss after left ATR is also predicted by poor seizure control after surgery,[53] more extensive resection,[26] male sex (hypothesized to result because women have a more bilateral representation of memory),[62] and older age at surgery.[30] The latter finding is presumed to reflect reduced plasticity or lower compensatory reserve in older adults.[1] Finally, individuals with moderate depressive symptoms before surgery are at greater risk of verbal memory decline following left ATR; this finding is hypothesized to reflect reduced compensatory reserve.[8] Table 1 summarizes the presurgical predictors of postsurgical memory decline.

Memory After Right ATR

Visual memory impairments (for example, memory for faces or places) occur in approximately 6%–32% of individuals who undergo right ATR, depending on the type of visual memory. For example, a recent study showed that 1 in 5 individuals who underwent right ATR had a significant decline in face memory ability, whereas 1 in 4 individuals had a decline in memory for spatial locations.[15] As with verbal memory decline after left ATR, postsurgical visual memory loss is predicted by estimating the presurgical functional status of the tissue to be resected. Postsurgical visual memory loss after right ATR is predicted by greater presurgical right medial temporal lobe activation in response to a nonverbal task on fMRI,[31] a relatively larger right hippocampus compared with the left hippocampus,[63] later age at seizure onset,[21] and intact presurgical visual memory ability on neuropsychological[20] or Wada testing.[42] Other predictors include side of surgery (nondominant temporal lobe),[15] larger right lateral neocortex and mesial temporal excision,[37] poor postoperative seizure control,[16] and pathology of the resected tissue (atypical hippocampal sclerosis).[65] Besides visual memory, right ATR is found to impair olfactory discrimination, identification, and recognition memory abilities.[45]

Language After Left ATR

Word-finding difficulties also occur after ATR to the language-dominant hemisphere. The most common approach to assessing word-finding difficulties, confrontation naming (also referred to as semantic memory), evaluates general facts and meanings acquired through experience. Between 29% and 54% of individuals who undergo dominant, left ATR show significant word-finding difficulties after surgery.[58] Postoperative word-finding difficulties are more likely to occur with more extensive resection of lateral temporal cortex,[29] which is one area that stores semantic knowledge.[24] Other predictors of postoperative word-finding difficulties include an absence of hippocampal sclerosis or other imaging abnormalities before surgery,[11] MR tractography showing more lateralized white matter tracts in the language-dominant hemisphere,[48] fMRI temporal lobe laterality index,[51] the absence of risk factors for seizures (for example, febrile seizures in childhood),[56] cessation of language in tissue to be resected during intraoperative electrical stimulation mapping,[23] and better presurgical naming ability.[10] Semantic knowledge acquired later in life is the most vulnerable to loss after surgery.[4]

Later age at seizure onset is also a valid predictor of naming decline.[50] Individuals who experience seizures beginning at a later age routinely have better presurgical naming ability, so they are at greater risk of naming difficulties after dominant ATR. Schwarz et al.[56] found that individuals who had seizure onset at 15 years of age or older were more likely to experience word-finding difficulties than those whose seizures started earlier. It may be that individuals with earlier age at seizure onset have less to lose after surgery because naming ability is already impaired or, alternatively, that brain functions have had the opportunity to reorganize in individuals whose seizures began early in life.

We recently conducted a study to evaluate the risk of naming decline after surgery as a function of age across the lifespan.[14] We divided a sample of 229 individuals who underwent unilateral ATR (118 left and 101 right) into 5 groups (age at seizure onset < 10, 10–19, 20–29, 30–39, or ≥ 40 years). Results showed that the risk of naming decline after left ATR increased as a function of patient age at seizure onset, especially in middle adulthood (see Fig. 1). Over 60% of patients who had disease onset beginning after the age of 40 years showed a significant decline in

TABLE 1: Predictors of memory outcome after ATR

Predictors of Verbal Memory Decline	Predictors of Visual Memory Decline
dominant, lt ATR	nondominant, rt ATR
greater pre-ATR lt temporal lobe fMRI activation	greater pre-ATR rt temporal lobe fMRI activation
absence of hippocampal sclerosis	larger rt hippocampus
good preop verbal memory	good preop visual memory
good preop Wada verbal memory w/ rt-side injection	good preop Wada visual memory w/ lt-side injection
no asymmetry in activation on PET scan	later age at seizure onset
later age at seizure onset	poor postop seizure control
poor postop seizure control	larger rt-lateral neocortex & mesial temporal excision
more extensive resection	pathology of resected tissue (atypical sclerosis)
male sex	
older age at op	
preop major depression	

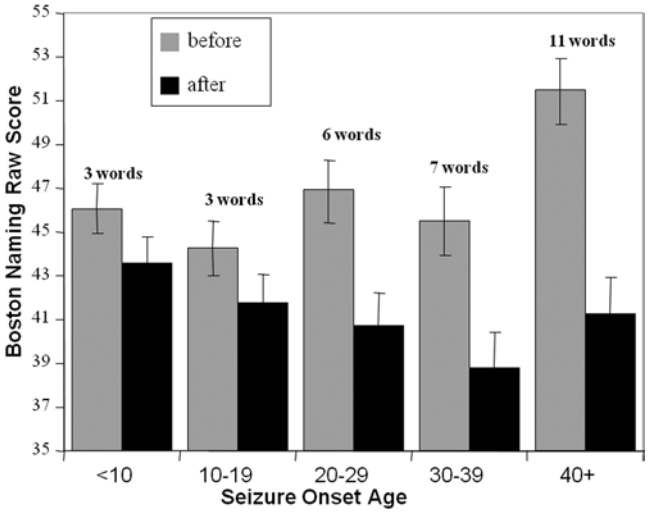

Fig. 1. Graph showing the reduction in naming ability (rounded to closest number of words) from before to after a left ATR stratified by age group (age at which patients began to have seizures). The results show that older age at seizure onset is a risk factor for greater naming decline (11-word decline or 19% reduction in performance) after left ATR. The *bars* represent the mean scores for the different age groups.

naming ability after left ATR (Fig. 2), whereas less than 5% in the same age at seizure onset group showed decline after right ATR. Follow-up analyses demonstrated that it was not that older surgical candidates were more likely to show a decline in naming after surgery but rather older age at seizure onset increased the risk of postsurgical decline.

Executive Function After Frontal Lobe Resection

The primary predictor of any impairment after frontal lobe resection is the location of surgery. Specific neurological deficits occur when resection involves the primary motor cortex, supplementary motor area, frontal eye fields, Broca area, dorsolateral prefrontal cortex, orbitofrontal cortex, or operculum. Motor and executive functioning impairments are the hallmark deficits associated with frontal lobe resection. Postoperative executive functioning declines following frontal lobe resection may include changes in attention and multitasking, fluency, response inhibition, concept formation, or problem solving.[7] Left dorsolateral frontal lobe resection is associated with

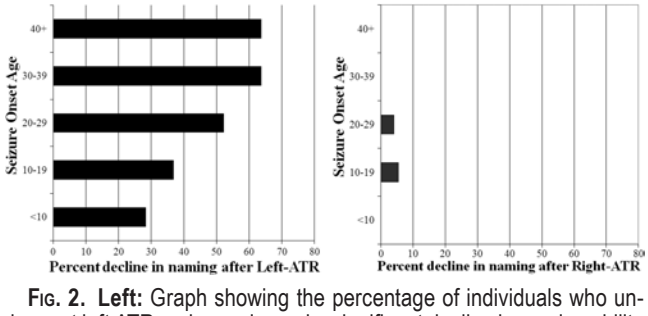

Fig. 2. Left: Graph showing the percentage of individuals who underwent left ATR and experienced a significant decline in naming ability divided by age group (age that patients began to have seizures). Over 60% of patients with seizure onset later than 30 years of age had a significant decline in naming ability after left ATR. **Right:** Graph showing the results after right ATR.

postoperative phonemic fluency impairment, and right frontal lobe resection is associated with postoperative visual fluency impairment, particularly when the resection is extensive and includes frontal pole and orbitofrontal cortex.[36,49] Resection that includes dorsolateral prefrontal cortex can also lead to working memory and multitasking deficits.[40] Left-sided resection of frontal premotor and supplemental motor areas is associated with transient expressive aphasia. Larger resections in either hemisphere also contribute to postoperative disinhibition and perseverative behavior.[27,49] Odor identification and odor memory impairments occur following resection of orbitofrontal cortex.[38] There is also literature demonstrating executive dysfunction after ATR, which is hypothesized to result from a disconnection between frontal and temporal lobe networks.[2] Interestingly, a recent case study found that right posterior inferior frontal lobe resection led to transient hemispatial neglect.[60]

Other predictors of executive impairments after frontal lobe resection include intact presurgical executive functioning,[27] continued seizures after surgery,[27] and presurgical depressed mood.[13]

Deficits After Occipital and Parietal Lobe Resection

There is a paucity of research evaluating the cognitive sequelae associated with resection of occipital and parietal lobe seizure foci, and most available studies are based on small samples of heterogeneous patient populations.[5,7] Given this situation, we focus on summarizing neurological deficits that frequently accompany resections within the occipital or parietal lobes. Patients with occipital lobe epilepsy often have visual symptoms even prior to epilepsy surgery, including visual agnosia, visual hallucinations or illusions, and contralateral visual field defects.[18,41,47] Visual-cognitive difficulties after occipital lobe resection are usually attributed to damage to optic radiations and other visual processing areas during surgery. A recent report indicated that 50% of patients had new visual deficits following occipital lobe resection with 17% developing quadrantanopia or hemianopia.[61] In one study, 4 of 12 patients who underwent occipital lobe resection sustained new visual field cuts following surgery, and an additional 2 patients reported postoperative change in motion detection ability (that is, with damage to area V5/MT).[33] In a case study involving a 23-year-old woman, right-sided resection at the inferolateral temporo-occipital junction led to transient prosopagnosia, which resolved 7 days after the surgery.[46] Another case study described new-onset implicit visual memory and font-specific priming deficits after a right occipital lobe resection involving Brodmann areas 17 and 18 and a portion of area 19.[19,64]

Parietal lobe epilepsy is associated with visual perceptual and spatial-constructional impairments, agnosia, decreased tactile discrimination ability contralateral to the side of surgery, left-right orientation confusion, hemineglect, and visual illusions.[12,34,52] Resection of the parietal lobe can also lead to anomia, agraphia, alexia, apraxia, acalculia, and face-perception difficulties in a small percentage of patients.[39,52] One study demonstrated that resec-

tion within posterior temporal-occipital-parietal areas for treatment of epilepsy resulted in a postoperative decline in nonverbal IQ, but not verbal IQ, as nonverbal skills rely to a greater degree on visual processes.[43]

Conclusions

Cognitive morbidity following resection for treatment of intractable epilepsy is associated with several factors, including location and extent of resection, disease characteristics, patient demographic characteristics, and functional status of the tissue to be resected. Preoperative neuropsychological assessment is useful for creating a risk-benefit profile when estimating the possible postsurgical decrements associated with excision of eloquent areas of the brain versus the benefits of seizure freedom. Presurgical counseling, as well as postsurgical rehabilitation referrals, could diminish any distress associated with deficits that may occur after resection of temporal and extratemporal seizure foci.[28,55]

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Epilepsy surgery in tuberous sclerosis: a review

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Seizures are the initial manifestation of tuberous sclerosis complex (TSC) in 90% of individuals. The prevalence of epilepsy in TSC is 80%–90% with a large proportion refractory to antiepileptic drugs. A review of the literature of epilepsy surgery in TSC demonstrates impressive success rates for seizure-free outcomes. These studies describe a number of novel noninvasive methods for seizure localization including PET, SPECT, and magnetoencephalography. Additionally, there is a subset of patients with TSC with bilateral, multifocal, or generalized epileptiform discharges that would have previously been excluded from resection. New developments in neuroimaging and invasive monitoring with intracranial electrodes are useful methods in identifying an epileptogenic tuber in these individuals with refractory epilepsy. The authors offer a survey of the literature and description of these methods. Additionally they present an illustrative case of ictal SPECT and intracranial electroencephalography used in the preoperative evaluation of a 10-year-old girl with intractable seizures and TSC. This patient ultimately underwent resection of an epileptogenic region within the occipital lobe.
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Key Words • **tuberous sclerosis** • **seizure** • **epilepsy** • **localization** • **outcome**

Tuberous sclerosis complex is an autosomal dominant disorder with variable effects on the CNS, as well as other tissues and organs. The pathognomic cerebral lesions are cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas. Development of these lesions occurs when spontaneous or inherited mutations in the *TSC1* or *TSC2* loci, encoding the protein products hamartin and tuberin, lead to aberrant neuronal differentiation, proliferation, and organization.[12] Seizures are the initial manifestation of the disorder in 90% of individuals and the prevalence of epilepsy in TSC is reported to be 80%–90%.[26] Seizure onset is typically within the first 12 months of life. As many as one-third of these individuals will present with infantile spasms, although a number of different seizure types are frequently observed. In a study of 361 patients with TSC, epileptiform abnormalities were appreciated in 78%. Within this set of individuals, focal spike and wave discharges were observed in 35%, multifocal discharges in 25%, generalized spike and wave in 8%, and hypsarrhythmia in 22%.[34] The pathogenesis and molecular underpinnings of epilepsy in tuberous sclerosis are not well defined. Abnormal expression of glutamate and γ-aminobutyric acid receptors in dysplastic neurons and giant cells of cortical tubers has been described,[35] as well as impaired glutamate transport in astrocytes in a mouse model of TSC.[36] Interestingly, not all tubers are associated with electroencephalographic abnormalities. Imaging studies frequently reveal tubers for which there is no epileptiform correlate. Conversely, other studies have demonstrated localized epileptiform activity without a corresponding structural lesion. Using intracranial electrocorticography in 3 patients, Major et al.[23] found that the epileptiform discharges emanated from the surrounding cortex rather than the tuber itself. The number, size, location, and morphology of cortical tubers have been found to influence seizure severity and degree of cognitive impairment.[11,13,20,30]

Unfortunately, seizures associated with tuberous sclerosis are often resistant to treatment with antiepileptic medications. The rate of epilepsy refractory to medical therapy in TSC is 50%–80%,[1,16] typically developing by the age of 2. Other studies have demonstrated a positive correlation between the frequency and duration of seizures and the degree of mental retardation.[19] Effective treatments to eliminate or reduce the number of seizures are essential to improving functional outcomes. Since the

Abbreviations used in this paper: AMT = α-11-*C*-methyl-L-tryptophan; EEG = electroencephalography; MEG = magnetoencephalography; TSC = tuberous sclerosis complex.

first published patient series of epilepsy surgery in TSC at the Montreal Neurological Institute in 1966,[27] surgery has proven to be an important treatment option for intractable seizures. From a systematic review of the literature, the rates of seizure-free outcome or reduction > 90% in individuals with refractory epilepsy were 57% and 18%, respectively.[17] The range of seizure-free outcomes reported in the reviewed literature is 22%–67%. Findings associated with improvement following surgery include a single cortical tuber, focal EEG abnormalities, and focal seizures.[1] Tonic seizures, moderate to severe mental retardation, and older age at the time of resection have been associated with seizure recurrence following epilepsy surgery.[17,37] There does not appear to be a difference in outcome following resection of temporal compared with extratemporal tubers.[4] Aside from the success of epilepsy surgery in seizure control, there are long-term benefits predicted for developmental and cognitive outcomes. Since the first descriptions of epilepsy surgery in TSC, the methods to localize epileptogenic tubers and resection have become increasingly sophisticated. In this paper we survey the literature describing resection in TSC (Table 1), focusing on recent developments in preoperative evaluation and seizure localization. An illustrative case is also presented.

Epilepsy Surgery in TSC

The first series describing resection in TSC relied on CT or MRI and surface EEG for localization. Focal interictal or ictal abnormalities on EEG correlated with a single radiographic lesion that was targeted for lesionectomy or focal resection.[6,7] At the time of surgery, electrocorticography was frequently performed to assist in defining the area of resection. In these first reports, the patients selected had focal electroencephalographic discharges with little ambiguity in localization. In a study of 18 patients by Guerreiro et al.,[14] 12 patients had focal or regional EEG abnormalities directing resection. Six of the patients, however, had multiple lesions or nonlocalizable epilepsy due to generalized EEG abnormalities. These patients ultimately underwent corpus callosotomy rather than focal resection with improvement in seizures. Avellino et al.[4] selected 11 patients for resection. Six patients had focal epileptiform discharges on preoperative scalp EEG. Five patients exhibited multifocal or generalized abnormalities and required intracranial monitoring with subdural grid and strip electrodes for localization. All patients were subsequently candidates for focal resection. Seven of the 11 patients had an electroencephalographic abnormality that corresponded to a tuber on MRI. The other 4 patients had no radiographic abnormal-

TABLE 1: Methods used in the preoperative evaluation of TSC before resection*

Authors & Year	No. of Patients	Neuroimaging Modality	MEG	Scalp EEG	Intracranial EEG	No. Seizure Free (%)
Aboian et al., 2011	6	MRI/SISCOM	no	yes	no	3 (50)
Carlson et al., 2011	14	MRI/PET/SPECT	yes	yes	yes	7 (50)
Kassiri et al., 2011	10	MRI	no	yes	no	10 (100)
Moshel et al., 2010	15	MRI/PET/SPECT	no	yes	no	12 (80)
Wu et al., 2010	18	MRI/PET	yes	yes	yes	12 (67)
Major et al., 2009	3	MRI	no	yes	yes	2 (67)
Sugiyama et al., 2009	8	MRI	yes	yes	no	6 (75)
Chandra et al., 2006	11	PET & MRI/DTI	no	yes	no	8 (73)
Jansen et al., 2006	3	MRI	no	yes	no	2 (67)
Vigliano et al., 2002	4	MRI	no	yes	no	2 (50)
Weiner et al., 2006	23	MRI/PET/SPECT	yes	yes	yes	21 (84)
Asano et al., 2005	8	MRI/PET	no	yes	yes	6 (75)
Kagawa et al., 2005	17	MRI/AMT-PET	no	yes	yes	12 (70)
Lachhwani et al., 2005	17	MRI	no	yes	no	11 (65)
Karenfort et al., 2002	8	MRI/PET	no	yes	yes	3 (38)
Romanelli et al., 2002	2	MRI/SPECT	no	yes	yes	1 (50)
Ohta et al., 2001	1	MRI/PET	no	yes	no	0
Asano et al., 2000	7	MRI/PET (AMT/FDG)	no	yes	yes	5 (71)
Koh et al., 2000	11	MRI/SPECT	no	yes	yes	9 (82)
Guerreiro et al., 1998	12	CT/MRI	no	yes	no	7 (58)
Avellino et al., 1997	11	CT/MRI	no	yes	yes	6 (55)
Baumgartner et al., 1997	4	MRI	no	yes	no	1 (25)
Bebin et al., 1993	9	CT/MRI	no	yes	no	6 (67)
Bye et al., 1989	1	CT	no	yes	no	0
Perot et al., 1966	7	CT	no	yes	no	3 (43)

* The length of time until follow-up varied in each study. Abbreviation: SISCOM = subtraction ictal SPECT coregistered to MRI.

ity, although the resected tissue had histological features consistent with a tuber.

In these initial studies resection of a dominant epileptogenic focus resulted in elimination or reduction of seizures. The series presented above, however, were limited largely to patients with focal ictal epileptiform discharges or a single radiographic lesion. Localization and surgical planning in this cohort presents several unique obstacles in epilepsy surgery. Affected individuals will frequently have several seizure semiologies. Furthermore, epileptogenic tubers are often multifocal, involve both hemispheres, and reside adjacent to or within eloquent cortex. Resection of a dominant seizure focus potentially allows for a secondary focus to emerge, leading to seizure recurrence. Recognizing these potential limitations to seizure localization and resection, investigators have reported a number of novel techniques in neuroimaging and neurophysiology. The armamentarium for preoperative evaluation now includes diffusion-weighted and diffusion-tensor MRI, functional MRI, SPECT, FDG and AMT-PET, MEG, and high-resolution EEG.

Novel Methods for Preoperative Evaluation in TSC

Identification of cortical tubers on MRI with T2-weighted and FLAIR sequences is well described. Unfortunately, this does not allow for differentiation between epileptogenic and nonepileptogenic lesions. A recent report[15] demonstrated that epileptogenic tubers showed a significant increase in the apparent diffusion coefficient relative to nonepileptogenic tubers and normal cortex. In a series of 15 patients, Chandra et al.[9] demonstrated that epileptogenic tubers had increased diffusion-tensor imaging–apparent diffusion coefficients in subtuber white matter relative to nonepileptogenic tubers. More impressively, the authors found that the largest volume of hypometabolism on FDG-PET/MRI–coregistered images corresponded to epileptogenic tubers. The tuber volume measured by MRI was not statistically significant between epileptogenic and nonepileptogenic tubers. Tubers that were associated with epileptiform discharges on scalp EEG were associated with an increased volume of hypometabolism on FDG-PET. However, the ability to identify epileptogenic tubers was increased with the FDG-PET/MRI–coregistered images correlating with the epileptogenic tuber removed at the time of surgery in 88% of patients. Similarly in a report by Wu and colleagues,[37] a subset of patients who were not initially considered surgical candidates were able to undergo focal resection following localization with FDG-PET/MRI coregistration.

In addition to FDG-PET, other studies have examined the use of AMT-PET in localization of epileptogenic tubers. The compound AMT is a tracer of serotonin synthesis, and its use in studies of epilepsy is based on the observation of increased serotonin concentration in resected epileptogenic cortex. Epileptogenic tubers have been found to have increased AMT uptake compared with surrounding cortex and nonepileptogenic tubers.[2,10] In an analysis of 17 patients selected for resection, AMT-PET studies were included in the preoperative evaluation, and 77% of the cortical tubers with increased AMT uptake were within the EEG-defined region. Of those patients with a single tuber that exhibited AMT uptake, the tuber was always within the electroencephalographic region of interest. For those with multiple areas of increased tracer uptake, the lesion with the greatest uptake correlated with the epileptogenic tuber. In 1 patient, increased AMT uptake was observed in the cortical tissue adjacent to a tuber. This tissue was found to have cortical dysplasia and balloon cells on histological analysis.[18]

An advantage of PET relative to other functional neuroimaging techniques is that it is performed in the interictal state; obtaining an ictal SPECT scan is often labor intensive and difficult. However, a number of studies have established a role for ictal SPECT in the localization of epileptogenic regions in patients with tuberous sclerosis complex. Koh et al.[21] found areas of hyperperfusion on ictal SPECT in 10 of 18 patients that corresponded to the region of seizure onset defined by scalp EEG. Another group used subtraction ictal SPECT coregistered to MRI in the evaluation of 6 patients with TSC. This technique is believed to improve the interpretation and accuracy of ictal SPECT. Intensity differences between the interictal and ictal SPECT greater than 2 standard deviations are coregistered with the MRI. Five of the 6 patients had multiple tubers on MRI and the ictal scalp EEG was localizing in 3 patients, lateralizing in 1, and generalized in 2. Five of the patients had a dominant region of hyperperfusion on subtraction ictal SPECT coregistered to MRI that was used in defining the area of resection. The 2 patients who underwent complete resection of the hyperperfused region were seizure free postoperatively.[1]

The use of MEG has been described in the evaluation of patients with TSC. It has been proposed that source localization may be more accurate with MEG than EEG. In a recent report, detection of a single seizure focus was greater with MEG than high resolution EEG in the same cohort. Additionally, the epileptogenic foci were closer to the presumed epileptogenic tubers with MEG when these results were superimposed on MRIs.[16] In a study of noninvasive testing using magnetic source imaging and FDG-PET, resection that included the magnetic source imaging dipole clusters was associated with seizure-free outcomes. In 75% of patients, MEG confirmed the localization from scalp EEG. In 10 patients with hemispheric or generalized ictal EEG onset, magnetic source imaging was localizing in 8 patients.[37] As in other areas of epilepsy research and surgery, MEG is developing an increased role in seizure localization.

Invasive Intracranial Monitoring

A number of patients with TSC and intractable seizures have nonlocalizable or nonlateralizing ictal and interictal EEG findings. For these individuals, MRI studies frequently reveal numerous and bilateral cortical tubers. Additional noninvasive testing such as PET, SPECT, and MEG may offer inconsistent results with no clear epileptogenic focus. Traditionally, these patients were not considered surgical candidates. Recent studies have ad-

dressed this patient population, analyzing effective methods of epileptogenic localization. In 1 recent study, 20 patients with nonlocalizable epilepsy underwent implantation of bilateral subdural strip and depth electrodes. The results of the intracranial monitoring identified epileptogenic regions amenable to resection in 15 of 20 patients; 5 had nonlateralizable epilepsy despite intracranial monitoring. Fourteen of the patients with epileptogenic foci underwent resection, with 50% of the patients becoming seizure free.[8] An added benefit to the use of intracranial electrodes for monitoring is the ability to perform cortical mapping when an epileptogenic region is in proximity to eloquent cortex.[28] In addition to monitoring with intracranial electrodes, this group has advocated multistage, 2- or 3-step resections. In select patients, intracranial electrodes are once again inserted at the time of initial resection. This method may reveal residual or secondary epileptogenic foci useful in directing additional and aggressive resections.[29,33]

Illustrative Case

This female patient with tuberous sclerosis developed seizures at 3 years of age. The predominant seizure semiology was defined by an aura of dizziness or visual blurring, followed by tonic eye and head deviation to the right, with or without secondary generalization. Other features of her seizures included variable paresthesias of the right and left hand, drop seizures, and absence seizures. The patient described visual phenomenon of geometrical shapes and flashing lights. Her seizures were initially controlled with valproic acid. After approximately 18 months of monotherapy, her seizures recurred and were intractable to multiple antiepileptic drugs including oxycarbazepine, carbamazepine, levetiracetam, ethosuximide, vigabatrin, gabapentin, and rapamycin. The patient presented to our institution at 10 years of age for formal surgical evaluation.

Interictal scalp EEG demonstrated multifocal discharges emanating from both temporal lobes (right greater than left) and bicentral regions. The polyspike and spike wave discharges were more frequent within the right hemisphere, with generalized polyspikes occurring during sleep. An ictal recording revealed onset of activity that came from the bilateral frontal and vertex regions.

Neuroimaging studies included MRI and SPECT. Numerous tubers and subependymal nodules were visualized on MRI (Fig. 1). There were no perfusion abnormalities on SPECT in the interictal state. The ictal study demonstrated an intense increase in perfusion to portions of the posterior right parietal, temporal, and occipital lobe (Fig. 2). From neuropsychiatric testing at the age of 6, her full scale IQ was 89, verbal comprehension index was 89 (low average), and perceptual reasoning was 90 (average range).

Considering that these initial studies were nonlocalizing, and the scalp EEG nonlateralizing, the patient underwent monitoring using bilateral intracranial electrodes. Subdural strip electrodes were positioned over the left temporal, left frontal, and right temporal convexity. Additionally, a 4 × 8 contact grid was inserted over the right parietooccipital region with interhemispheric coverage. Several ictal recordings were obtained during the period of monitoring with localization to the right occipital region (Fig. 3). Cortical mapping was performed with stimulation of this region replicating the visual phenomenon that she had described previously.

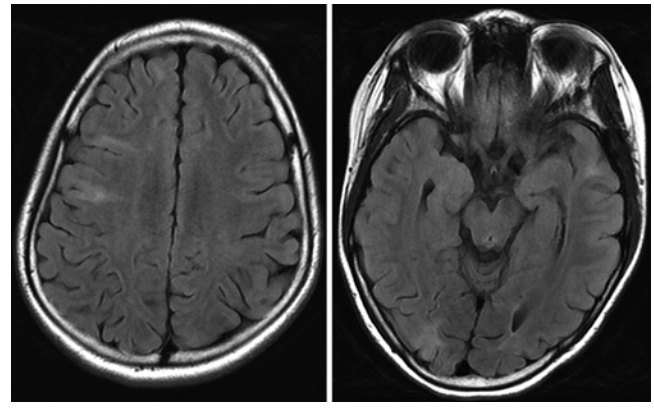

Fig. 1. Axial MRI/FLAIR sequences demonstrating multiple cortical tubers, as well as the right occipital tuber that was ultimately resected following evaluation.

After sufficient data collection, the patient underwent a partial resection of the right occipital lobe. Review of the pathology demonstrated that the tissue from this region was a cortical tuber. Postoperatively the patient was neurologically intact. Four months following surgery the patient remains seizure free. This case demonstrates the utility of using multiple modalities in the preoperative evaluation of patients with tuberous sclerosis. The bilateral multifocal and generalized discharges on scalp EEG and ictal SPECT did not localize a resectable epileptogenic focus. In this patient, the use of intracranial electrodes was an essential component in identifying a seizure focus and tailoring the resection.

Discussion

Seizures are a predominant manifestation of TSC and frequently prove refractory to medical therapy. The detrimental effects of frequent and uncontrolled seizures on childhood development and cognition have been well described in individuals with TSC. An increasing number of studies have demonstrated that resection of epileptogenic regions offers a significant benefit in seizure reduction or elimination. A number of features unique to TSC complicate epilepsy surgery including bilateral multifocal or generalized epileptiform abnormalities, often extratemporal location, and the potential for secondary epileptogenic foci to appear following resection of a dominant lesion. A number of novel noninvasive methods have been used in the preoperative evaluation as discussed in this review. Successful surgical outcomes have been observed with all of the methods described as noted by the outcomes reported in Table 1. Each has limitations and none is able to differentiate epileptogenic and nonepileptogenic tubers in all patients. What is clear from review of the literature is that more than 1 method should be used in each patient to confirm and better define an

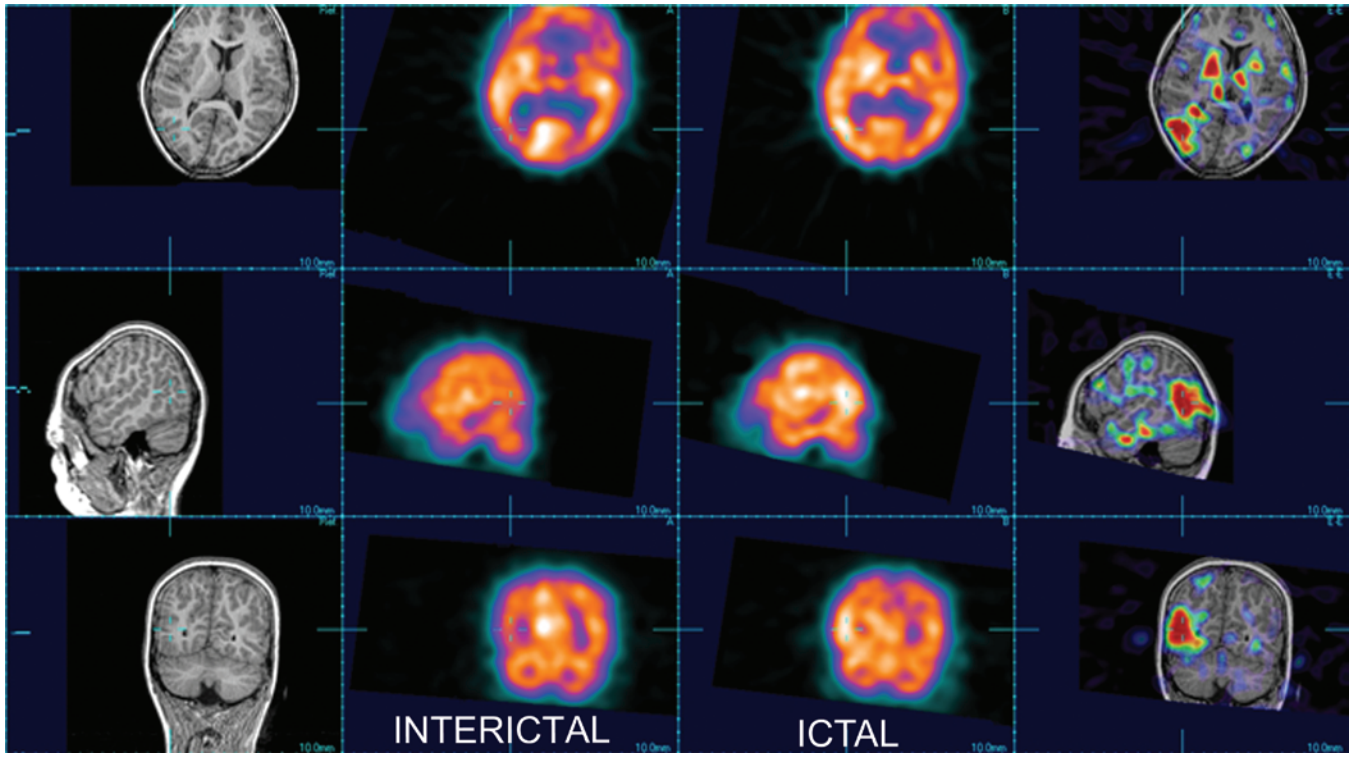

Fig. 2. Results from interictal and ictal SPECT demonstrating the region of hyperperfusion in the right occipital lobe *(upper row axial, center row sagittal, lower row coronal)*. The ictal SPECT has been coregistered and fused (gray scale) with the T1-weighted MRI (first column) in the final column.

area for resection. Although noninvasive techniques such as MRI, PET, SPECT, or MEG may be sufficient to direct resection in some patients, invasive monitoring with intracranial electrodes is invaluable in expanding the number of surgical candidates. Epilepsy surgery is a fascinating and exciting treatment for intractable seizures in tuberous sclerosis based on the potential benefits to patients, the diagnostic dilemmas it poses, and the need for further developments.

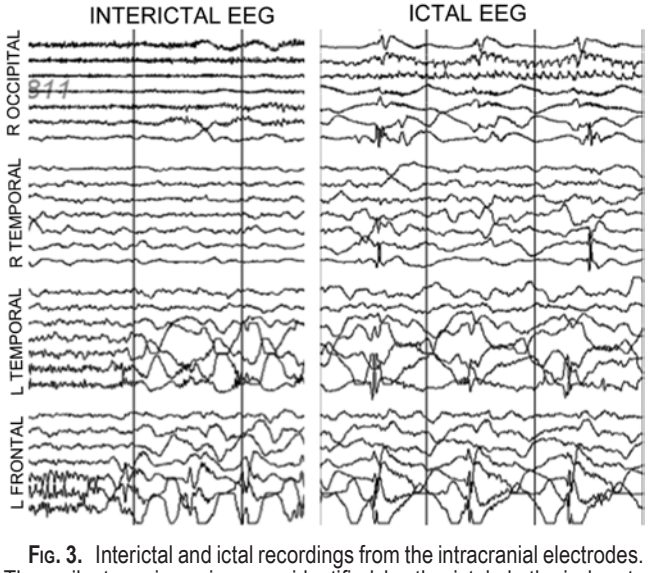

Fig. 3. Interictal and ictal recordings from the intracranial electrodes. The epileptogenic region was identified by the ictal rhythmic bursts (marked) in the contacts overlying the right occipital lobe.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Roberts. Acquisition of data: Morse. Drafting the article: Evans. Critically revising the article: Roberts. Administrative/technical/material support: Roberts.

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Surgical techniques for investigating the role of the insula in epilepsy: a review

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Intracranial electroencephalography monitoring of the insula is an important tool in the investigation of the insula in medically intractable epilepsy and has been shown to be safe and reliable. Several methods of placing electrodes for insular coverage have been reported and include open craniotomy as well as stereotactic orthogonal and stereotactic anterior and posterior oblique trajectories. The authors review each of these techniques with respect to current concepts in insular epilepsy.
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Key Words • **intracranial electrodes** • **epilepsy surgery** • **epilepsy** • **insula** • **stereotaxy**

Insular epilepsy has been the subject of increasing investigation over the past decade, but the concept of seizures arising within the insula was in fact first proposed over half a century ago on the basis of intraoperative electrocorticographic recordings in patients undergoing epilepsy surgery,[9] findings that went on to be replicated several years later by Wilder Penfield.[19] There followed several decades of anecdotal reports of seizures associated with insular lesions, including tumors and cavernomas,[4,6,10,23] but owing perhaps to hazardous surgical anatomy and often unfavorable outcomes reported with insular resection,[27] there remained little focused investigation of the insula in ictal onset for many years. Recently, however, several groups have reported experiences with the use of recording electrodes in the insula in patients with medically intractable epilepsy.[1,7,11–13,15,16,26] These studies have enabled semiological characterization of seizures that have an insular onset and demonstrated good outcomes with insula resections in patients with insular seizures, illustrating the important role of intracranial insular recording in the effective surgical treatment of insular epilepsy. Furthermore, they have used a number of techniques and trajectories to place recording electrodes into the insula.

Insular seizures confirmed by stereo-EEG are usually simple partial in nature, with common features being laryngeal discomfort, dysphonia, paresthesias, and somatomotor symptoms. They may additionally include hypermotor features mimicking frontal lobe seizures, visceral symptoms, or dysphasia mimicking temporal lobe seizures, and early somatosensory symptoms in the absence of laryngeal constriction mimicking parietal lobe seizures.[11,12]

With respect to the outcomes after insular resections based on seizure-onset localization with intracranial recording, several groups have reported good outcomes with insula-sparing resections of the frontal and temporal lobes in patients in whom the insula was identified as a site of secondary seizure propagation, as well as in those without insular involvement.[1,12,13] In addition, there have been reports of persistence of insular-onset seizures after temporal lobectomy[11,12] and of insular seizures clinically mimicking those encountered in temporal lobe epilepsy and nocturnal frontal lobe epilepsy.[25] Furthermore, when patients preselected using clinical seizure characteristics, scalp EEG recordings (with or without video correlation), MRI, SPECT, and PET undergo insular electrode recording, a seizure-onset zone specifically within the insula may be found in approximately 10%–20% of cases. These findings, as well as the functional connectivity of the insula to the orbitofrontal cortex, cingulate cortex, and temporolimbic structures,[4,6,9,14,18,27] mandate consideration of the insula's role (and potential intracranial EEG recording of the insula) not only in insular epilepsy but also in suspected frontal or temporal lobe epilepsy.

Abbreviation used in this paper: EEG = electroencephalography.

Finally, several methodologies have been described for placement of insular electrodes. Central to understanding the arguments for and against each approach is an informed consideration of the pertinent anatomy of the insula and surrounding structures.

Surgical Anatomy of the Insula

The anatomical features of the insula present unique challenges in surgical exposure for electrode coverage. The insula covers the lateral surface of the hemispheric core and has a triangular shape with its apex directed anterior and inferiorly toward the limen insula. The insula is encircled and separated from the frontal, parietal, and temporal opercula by a shallow limiting sulcus, the circular sulcus, which has superior, inferior, and anterior borders. The insula also has radially projecting sulci and gyri (directed superiorly and posteriorly) from the insular apex. The central sulcus is the deepest of these sulci and extends superoposteriorly, dividing the insula into anterior and posterior parts.[20] Accessing the insula, therefore, requires dissection of the sylvian fissure, retraction of potentially functional opercular cortex, and further dissection through M_2 middle cerebral artery branches on the surface of the insula.[32]

Human cadaveric and primate studies have demonstrated that the insula receives main afferents from the amygdala, the dorsal thalamus, and different cortical regions, particularly the sensory cortices and the auditory cortex. Most of these afferents terminate in the posterior granular part of the insula, whereas the ventral anterior agranular insula receives predominantly afferents from the limbic cortex, e.g. the entorhinal, perirhinal, posterior, and orbitofrontal cortices and the cingulate gyrus. In addition, the efferents of the ventral anterior insula reciprocate the afferents of the anterior insula, although this is not the case in the posterior insula. Relatively little is understood about the function of the insula, although several investigators have suggested it may play a role in secondary sensory processing, language and motor control, or higher autonomic control and as a component of the limbic system.[2,12,14] The anatomical connectivity described above and the seizure characteristics seen in documented insular epilepsy are in keeping with this concept.

Intracranial EEG Investigation of the Insula

The use of intracranial EEG to investigate seizure onset in patients with medically intractable epilepsy is well established,[3,21] and the role of the insula in seizure onset has received increasing interest over the past decade.[1,5,7,11–13,15,16,24,26,34] Several groups have published reports of intracranial monitoring electrodes implanted into the insula using a variety of methods (Table 1).[1,5,7,11–13,15,16,26] Broadly speaking, the electrodes may be intracerebral depth electrodes (located within the insula) or subdural strip electrodes (located on the insula surface), and may be placed stereotactically, with or without the use of a stereotactic frame, or under direct visualization. The techniques of electrode placement within or onto the insula may be categorized as follows: 1) craniotomy and direct visualization method, with or without frameless stereotactic neuronavigation; 2) stereotactic orthogonal method; 3) stereotactic posterior oblique electrode method; 4) stereotactic anterior oblique electrode method; and 5) combined stereotactic anterior and posterior oblique electrode method.

These approaches have been extensively described and each has potential advantages and disadvantages, which will be discussed.

Techniques of Electrode Placement

Craniotomy and Direct Visualization Method

The first strategy to be considered involves the placement of a depth electrode within the insula, or a strip electrode onto its surface, after craniotomy and dissection of the sylvian fissure, as described by several groups.[13,30] When this method is used, placement of the depth electrode within the insula may also be accompanied by stereotactic guidance.[13,30]

The advantages of this approach are that it allows the insular electrode placement to be efficiently combined with temporal and frontal convexity subdural grid placement if required. This is a relatively common scenario, and this technique enables concomitant electrode coverage of these regions and the opercular surface, for recording and for functional mapping. Furthermore, insular coverage by a depth electrode can provide coverage of both the medial and lateral portions of the insula, which may be difficult to achieve with parasagittal oblique trajectories. Finally, in cases eventually requiring surgery, the subpial depth electrodes can be used as surgical landmarks for insular resection.[17]

This strategy, on the other hand, can have important drawbacks and may not always be preferred. If subdural grid electrodes necessitating an ipsilateral craniotomy are not required, then performing a craniotomy to place insular electrodes alone is less efficient than other techniques. This method also carries an increased risk of vascular injury to the middle cerebral artery during dissection, as well as the risk of morbidity from frontal lobe retraction.[30] Insular coverage provided by a typical depth electrode placed in this manner is essentially orthogonal, with 2 contacts expected to reside within the insula per electrode.[30] This "contact-to-electrode" ratio is lower than that achievable via oblique trajectories and therefore necessitates placement of a greater number of electrodes to get a broad sampling of the insula.

This technique can be efficiently complemented with frameless stereotactic guidance[17,30] and potentially with robotic placement.[28] The use of stereotactic neuronavigation, while potentially increasing operative duration and cost, provides assistance with electrode trajectory to maximize contacts within the insula and neighboring regions, if desired, and avoidance of deeper structures such as the internal capsule.

Some groups have reported placing subdural strip electrodes over the insular cortex without neuronavigation after craniotomy and splitting of the sylvian fissure.[17] This strategy necessitates stable placement of the strip elec-

TABLE 1: Major studies describing techniques for placement of insular recording electrodes*

Authors & Year	No. of Pts	Electrode Placement	Electrodes in Insula	Contacts in Insula	Complications	Localization of Seizure/ Onset to Insula
Isnard et al., 2004	50	frame-based stereotactic orthogonal trajectory w/ teleangiography	mean 2.9/pt	not reported	not reported	6 (12%) of 50; onset solely in insula in 5 (10%) of 50
Ryvlin et al., 2006[26]	3	1 frame-based stereotactic orthogonal trajectory w/ teleangiography; 2 w/ stereotactic ant oblique trajectory	1/pt	mean 5, range 2–7	not reported	larger cohort undergoing monitoring; onset not reported
Afif et al., 2008	30	frame-based stereotactic ant &/or pst oblique trajectories	mean 1.2/pt	mean 7.5	none reported	5 (18%) of 30; onset solely w/in insula in 2 (6.7%) of 30
Malak et al., 2009	7	1 w/ orthogonal, frame-base stereotactic trajectory w/ teleangiography; 6 w/ depth electrodes placed under direct visualization	2/pt in most cases	2	1 pt w/ transient leg weakness	larger cohort undergoing recording; not reported
Park et al., 2009	6	1 strip electrode placed under direct visualization; 2 depth electrodes placed w/ frame-based stereotactic pst oblique trajectories; 3 depth electrodes (direct visualization w/ aid of image guidance)	3/pt under direct visualization; 1/pt placed stereotactically	strip electrode w/ 2 contacts; depth electrodes (2 for stereotactic, 4 for direct visualization)	none reported	larger cohort undergoing recording; not reported
Robles et al., 2009	9	frame-based stereotactic pst oblique trajectory	1/pt	>4 in all cases	none reported	larger cohort undergoing op; not reported
Desai et al., 2011	20	frame-based stereotactic oblique ant trajectory	mean 1.45/pt	mean 5.2/pt	none reported	2 (10%) of 20
Surbeck et al., 2011	19	16 w/ depth electrode placement under direct visualization; 3 w/ frame-based stereotactic, transfrontal, & transparietal trajectories	direct visualization: 1–3; stereotactic placement: 2	direct visualization: mean 3.5 (range 1–6); stereotactic placement: overall mean 8, 2–4 w/ transfrontal trajectory, 5–7 w/ transparietal trajectory	1 foot-drop due to migration of electrode; 1 dysphasia from opercular retraction	7 (37%) of 19

* Modified with permission from Desai et al.: **J Neurosurg 114:**1176–1186, 2011. Abbreviations: ant = anterior; pst = posterior; pt = patient.

trodes within a relatively narrow space, which is hindered by surrounding vasculature. Our own group at one time made recordings from the insula using strip electrodes, but we were not satisfied with the coverage and electrode stability and have since ceased using this strategy.

Stereotactic Orthogonal Approach

The stereotactic orthogonal, or transopercular, approach was originally described by Talairach and Bancaud[31] and has since been frequently used in various insular applications.[7,11,12] Of the stereotactic approaches to the insula, the orthogonal approach is historically the most well established. It involves the placement of multiple ipsilateral axially oriented electrodes into the insula using frame-based coordinates and has traditionally been facilitated by teleangiography, or newer 3D methods of angiography, to avoid middle cerebral artery branches.

The advantages of this approach include its relatively established use as a safe and efficacious method of accessing the insula and the ability to sample medial and lateral portions of the insula, as well as neighboring frontal and temporal opercula. The use of teleangiography meanwhile does not require computer-based registration.

The relative disadvantages include an inherent trajectory through a region of potentially eloquent cortex and numerous vascular structures; as such, the procedure requires accurate visualization of the middle cerebral artery, sylvian fissure, and sulcal vasculature.[8,32,33] Although this can be achieved using either teleangiography or stereotactically coregistered vascular imaging, this may be more time consuming than other stereotactic approaches and some surgeons consider it cumbersome. In addition, the orthogonal trajectory and the shape of the insula in this technique, like the above-mentioned open approach, result in relatively fewer contacts (n = 2) per electrode within the insula,[26] leading to a greater number of electrodes needing to be placed for sufficient insular coverage and further decreasing the technique's potential efficiency. Like all implantation methodologies, confirmation of contact localization on postoperative imaging (MRI or CT) is essential.

Stereotactic Posterior Oblique Approach

Several groups have described placing depth electrodes stereotactically using image-guided, frame-based, stereotactic oblique trajectories planned to minimize pial violations.[1,5,22,26,29,30] These oblique approaches have been facilitated by advances in stereotactic planning, visualization, and trajectory determination. These oblique trajectories may be posterior (transparietal) or anterior (transfrontal), and can potentially be performed with additional robotic assistance.[1]

The posterior approach, in which depth electrodes targeting the insula are placed through a parietal entry point, is the more commonly reported oblique trajectory (Fig. 1).[1,22,30] This approach carries the relative advantage of a trajectory through a relatively safe, usually noneloquent corridor. Unlike the open approach to electrode placement, this approach avoids the need for craniotomy, sylvian fissure dissection, and opercular retraction. Furthermore, in contrast to the stereotactic orthogonal approach, it does not require passing the electrodes through potentially eloquent cortex or through the dense vasculature of the sylvian fissure and the insular surface. A posterior trajectory also allows more proximal electrode contacts to be placed in the parietal lobe, which may be of use where there is concern of parietal involvement in seizure onset. The posterior trajectory also appears well tailored to the 3D shape of the insula, and the trajectory can almost approximate the long axis of the insula. This subsequently increases the number of contacts per electrode residing within the insula, using this trajectory, and potentially makes this a very efficient technique.

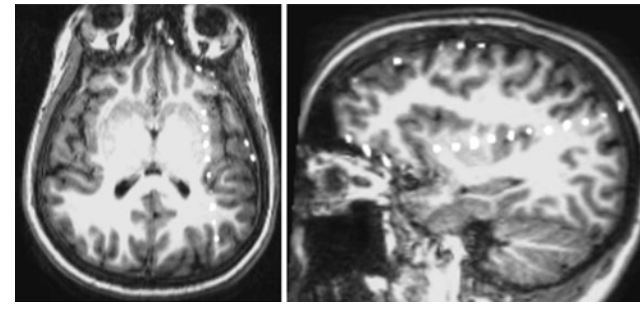

Fig. 1. Coronal **(left)** and sagittal **(right)** CT-MRI reconstructions demonstrating the posterior oblique trajectory for insular depth electrode placement.

The posterior oblique trajectory also has some potential drawbacks. It is necessarily performed stereotactically and requires sophisticated computerized registration, usually with stereotactic head frame placement. Using this trajectory also makes it difficult for coverage to span the entire mediolateral width of the insula, unlike the case with the orthogonal or open approach. Furthermore, several authors consider the approach to offer relatively limited coverage of the anterior insula.[1,30] Similar to other stereotactic approaches, this technique also carries the potential disadvantage of reliance on postoperative imaging to confirm correct electrode placement.

Stereotactic Anterior Oblique Approach

An alternative oblique trajectory is the transfrontal approach in which the depth electrode is placed through an anterior frontal entry point (Fig. 2). This approach has been described by several groups recently, including our own.[1,5,30]

Advantages of this technique include a relatively safe trajectory through usually noneloquent anterior frontal

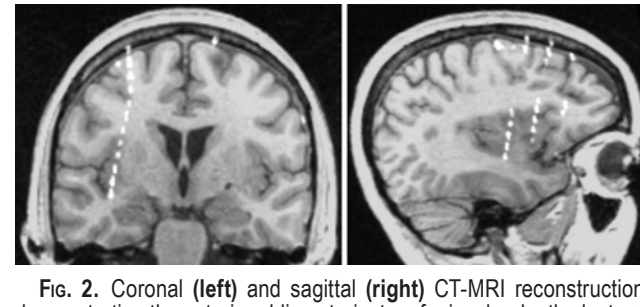

Fig. 2. Coronal **(left)** and sagittal **(right)** CT-MRI reconstructions demonstrating the anterior oblique trajectory for insular depth electrode placement.

cortex. In addition, the trajectory passes through the insula in a posteriorly angulated, approximately parasagittal plane, potentially allowing several contacts of a given electrode to reside within the insula. An additional advantage of this trajectory is that it provides added frontal coverage with more proximal contacts. This can be particularly useful in the relatively common scenario of ambiguity on the roles of both the insula and the frontal lobe in seizure onset.

Disadvantages of this technique, similar to the transparietal trajectory, include the relative reduction in mediolateral electrode contact coverage that can be achieved within the insula. Furthermore, like the transparietal trajectory, this technique requires computer-based registration, the placement of a stereotactic head frame, and is associated with concerns about the reliability of postoperative imaging in contact localization. Our own experience is that the latter has not proved problematic when postoperative high-resolution head CT scans are fused with preoperative MR images for reconstructions.[5] One further disadvantage of this trajectory, compared with the transparietal technique, is that the latter appears to facilitate greater contact coverage of the insula. Surbeck et al.[30] found that their use of the transfrontal trajectory resulted in 2–4 lead contacts being positioned within the insula whereas electrodes placed in the transparietal approach had a range of 5–7 contacts within the insula. Furthermore, a study by Afif et al.[1] documented a mean of 7.5 contacts per electrode within the insula when using either a transfrontal or transparietal trajectory (or both in some cases), whereas our own group's experience in using a transfrontal trajectory resulted in only 5.2 contacts within the insula per electrode.[5] The triangular shape of the insula and its essentially anteroposteriorly directed long axis may account for this, since the study by the aforementioned Grenoble group used a significant number of transparietal electrodes, compared with our own group, which used a transfrontal trajectory only. A prospective quantitative analysis of insular contacts achievable by each trajectory, however, remains to be performed. This technique may also provide reduced coverage of the posterior insula relative to the parietal approach, although its anterior insular coverage is likely superior.[1]

Combined Stereotactic Anterior and Posterior Oblique Approaches

Several groups have used a frame-based stereotactic approach and incorporated both transfrontal and transparietal oblique trajectories.[1,30] This strategy has the advantage of combining 2 relatively efficient, low-risk methods of electrode placement to enhance contact coverage within the insula and intervening frontal and parietal regions.[30]

The disadvantages of this method include the incrementally increased risk (for example, of hemorrhage and infection) associated with additional invasive subpial electrodes, in addition to the aforementioned drawbacks of oblique trajectories, namely a relative lack of mediolateral coverage, the requirement for computer-based registration and stereotactic frame placement, and potentially ambiguous postoperative imaging.

Conclusions

Intracranial EEG monitoring of the insula is an important tool in the clarification of the insula in medically intractable epilepsy and has been shown to be safe and reliable. Several methods of placing electrodes for insular coverage have been used, with subpial depth electrodes being the most common. These can be inserted during craniotomy and under direct visualization, with or without neuronavigation, or stereotactically using orthogonal or oblique trajectories. Each method has potential advantages and disadvantages and should be chosen accordingly.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Desai. Acquisition of data: Darcey. Analysis and interpretation of data: Desai. Drafting the article: Desai, Bekelis. Critically revising the article: Desai, Bekelis, Roberts. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Desai.

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The periinsular functional hemispherotomy

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The surgical treatment of refractory epilepsy has evolved as new innovations have been created. Disconnective procedures such as hemispherectomy have evolved. Presently, hemispherotomy has replaced hemispherectomy to reduce complication rates while maintaining good seizure control. Several disconnective techniques have been described including the Rasmussen, vertical, and lateral approaches. The lateral approach, or periinsular hemispherectomy, was derived from modifications on the functional hemispherectomy and involves removal of the temporal lobe mesial structures, exposure of the atrium via the circular sulcus, internal capsule transection under the central sulcus, intraventricular callosotomy, and frontobasal disconnection. The purpose of this article is to describe and illustrate in detail the anatomy and operative technique for periinsular hemispherotomy, as well as to discuss the nuances and issues involved with this procedure.
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Key Words • **epilepsy** • **hemispherectomy** • **periinsular hemispherotomy**

Disconnective procedures have been a common treatment for intractable epilepsy. For the last 2 decades disconnective procedures have evolved from anatomical hemispherectomy, to functional hemispherectomy, to hemispherotomy, which is the latest development in disconnective surgeries and represents a less invasive microsurgical procedure to disconnect the cortex of the affected hemisphere.

The move toward hemispherotomy started with Dandy's[4] technical description of anatomical hemispherectomy to treat brain tumors. Ten years later, McKenzie[13] applied the technique to manage intractable epilepsy. However, anatomical hemispherectomy was not popularized until a case series published by Krynauw[11] demonstrated good results with seizure control and cognitive development. Subsequently, anatomical hemispherectomy became a popular procedure in the treatment of unilateral hemispheric epilepsy-related syndromes (such as neonatal infarcts, hemimegalencephaly, Rasmussen encephalitis, and Sturge-Weber syndrome).[17,25,26] However, early and delayed complications from this procedure were increasingly reported, including excessive blood loss, metabolic imbalances, coagulopathy, superficial cerebral hemosiderosis, and development of hydrocephalus. Variations of the anatomical hemispherectomy technique were described to minimize the incidence of such complications, but hemidecortication and subdural space reduction techniques ultimately did not result in significant reduction of associated complications.[15,18]

In 1974, Rasmussen introduced the functional hemispherectomy, which is a surgical method that involves removing less cerebral tissue and disconnecting the remaining tissue. Functional hemispherectomy is meant to achieve the same physiological goal of anatomical hemispherectomy in terms of seizure control. The overall goals of any functional hemispherectomy to achieve a complete disconnection are resection of the medial temporal structures, disruption of the internal capsule and corona radiata, intraventricular corpus callosotomy, and disruption of the frontal horizontal fibers. Based on a recent review, disconnective procedures have been categorized as Rasmussen,[17] vertical,[5] and lateral approaches.[24] The lateral approach introduced in 1995 by Schramm et al.[20] and Villemure and Mascott[24] is also referred to as the periinsular hemispherotomy. Variations of the periinsular hemispherectomy have been proposed and include the transsylvian keyhole functional hemispherectomy by Schramm et al.[21] and the modified periinsular hemispherotomy by Shimizu and Maehara.[22]

The present study consists of a review and analysis of one the most recent technical variations of disconnective hemispherectomies. We adopted the technique described by Schramm et al. and Villemure and Mascott. The technique described here has been applied since 2008 to patients who were required to undergo a disconnective hemispherectomy for intractable epilepsy at Texas Children's Hospital, Baylor College of Medicine, in Houston, Texas.

The Periinsular Hemispherotomy: Technical Description

This periinsular hemispherotomy is performed while the patient is under general anesthesia and receiving endotracheal intubation. With the patient supine, all pressure points are well-padded, and a small roll is placed under the ipsilateral shoulder. The head is turned 90° to the opposite site and is held using Mayfield 3-point pin fixation. Neuronavigation is registered and can be helpful in delineating the skin incision and craniotomy. We favor a reverse "question-mark" shaped incision centered over the sylvian fissure (Fig. 1). The surgical exposure should span the sylvian fissure, allowing access to the anterior and posterior temporal lobes, the lateral aspect of the frontal lobe, and the parietal lobe. The incision extends inferiorly to the zygoma, allowing adequate exposure of the temporal lobe. The superior limb of the skin incision should be extended at least slightly above the superior temporal line. The craniotomy should extend superior and posteriorly enough to provide adequate access to the anterior horn, body, and atrium of the lateral ventricle (Fig. 1). The dura mater is then opened in a C-shape and reflected anteriorly. The disconnective procedure is carried out in several steps: 1) an amygdalohippocampectomy is performed with or without an anterior temporal lobectomy (Figs. 2 and 3); 2) a transcircular sulcus exposure of the ventricular atrium is made (Fig. 4); 3) a transection of the internal capsule around the basal ganglia and thalamus under the central sulcus is completed (Fig. 5); and the 4) intraventricular callosotomy (Fig. 6); 5) frontobasal disconnection (Fig. 7); and 6) insular aspiration are achieved.

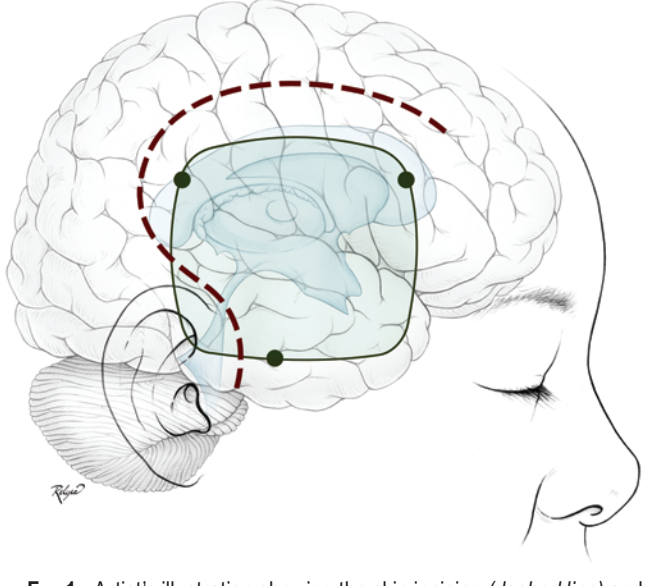

Fig. 1. Artist's illustration showing the skin incision *(dashed line)* and craniotomy *(shaded area)* for periinsular hemispherotomy. The reverse question-mark incision extends superiorly from the anterior portion of the superior temporal line and inferiorly to the zygoma. The surgical exposure should include the lateral aspect of the frontal and parietal lobes, the sylvian fissure, and the majority of the temporal lobe. Adequate access is necessary to visualize the entire lateral ventricle, including the anterior horn, body, and atrium.

Amygdalohippocampectomy With or Without Anterior Temporal Lobectomy

The initial step of a periinsular functional hemispherotomy depends on whether lateral temporal tissue is needed for pathological analysis. If tissue is required, the temporal portion of the procedure can be simplified by performing an anterior temporal lobectomy (Fig. 2). The initial incision is made along the superior temporal gyrus. The incision is inclined laterally, at a depth of 1 or 2 cm. The corticectomy is carried posteriorly to a distance of 4–4.5 cm from the temporal tip. The corticectomy is deepened into the whiter matter of the gyrus, angling slightly posteriorly until the temporal horn of the lateral ventricle is entered. The depth of the temporal horn from the cortical surface should be determined from the MRI scan and neuronavigation; it usually lies 3–3.5 cm from the surface. Once the ventricle is entered, a small cottonoid is placed in it. The neocortex is further released by extending the initial corticectomy along the superior temporal gyrus to the temporal tip and completing the orthogonal corticectomy to the floor of the middle cranial fossa. The lateral neocortex is then removed by dissection parallel to the cortical surface at the depth of the white matter just above the ventricle.

After the lateral neocortical resection is complete, the anterior tip of the temporal horn of the lateral ventricle is exposed. An incision is made from the tip of the ventricle to the temporal tip, and orthogonally to the lateral inferior pial edge. Each incision is extended to pia, and the pia over the dura is incised, resecting the parahippocampal cortex to obtain a specimen for pathological analysis. A subpial plane is then developed from the lateral edge medially until the carotid bifurcation is visualized thru the pia and the entorhinal sulcus is reached, confirmed either by inspection or by frameless stereotaxy. This specimen is taken as uncus. Caution should be used to maintain an intact pial membrane as a protective layer to avoid injury to the posterior cerebral artery and the third and the fourth cranial nerves lying deep to the subpial dissection. The amygdala is removed by resecting the tissue laterally and inferiorly to a plane drawn from the M_1 segment of the middle cerebral artery visualized thru the pia and the entrance of the anterior choroidal artery into the choroidal fissure (choroidal point). The hippocampus is resected by incising the ependyma over the blueish choroidal point (velum interpositum) between the hippocampus and the choroid plexus and extended inferiorly to the hippocampal fissure. A second incision is made inferior to the hippocampus down to the pial membrane and extended to the hippocampal fissure. The hippocampus is then elevated laterally, exposing the skeletonized hippocampal fissure and allowing it to be cauterized and cut away from the choroidal fissure and hippocampus, delivered as an intact specimen.

If a cortical specimen is not required, the periinsular hemispherotomy is begun by an extensive dissection of the sylvian fissure, exposing the circular sulcus (Fig. 3). The cortex of the inferior circular sulcus is resected to the white matter of the temporal stem, and this incision is deepened until entrance into the temporal horn of the

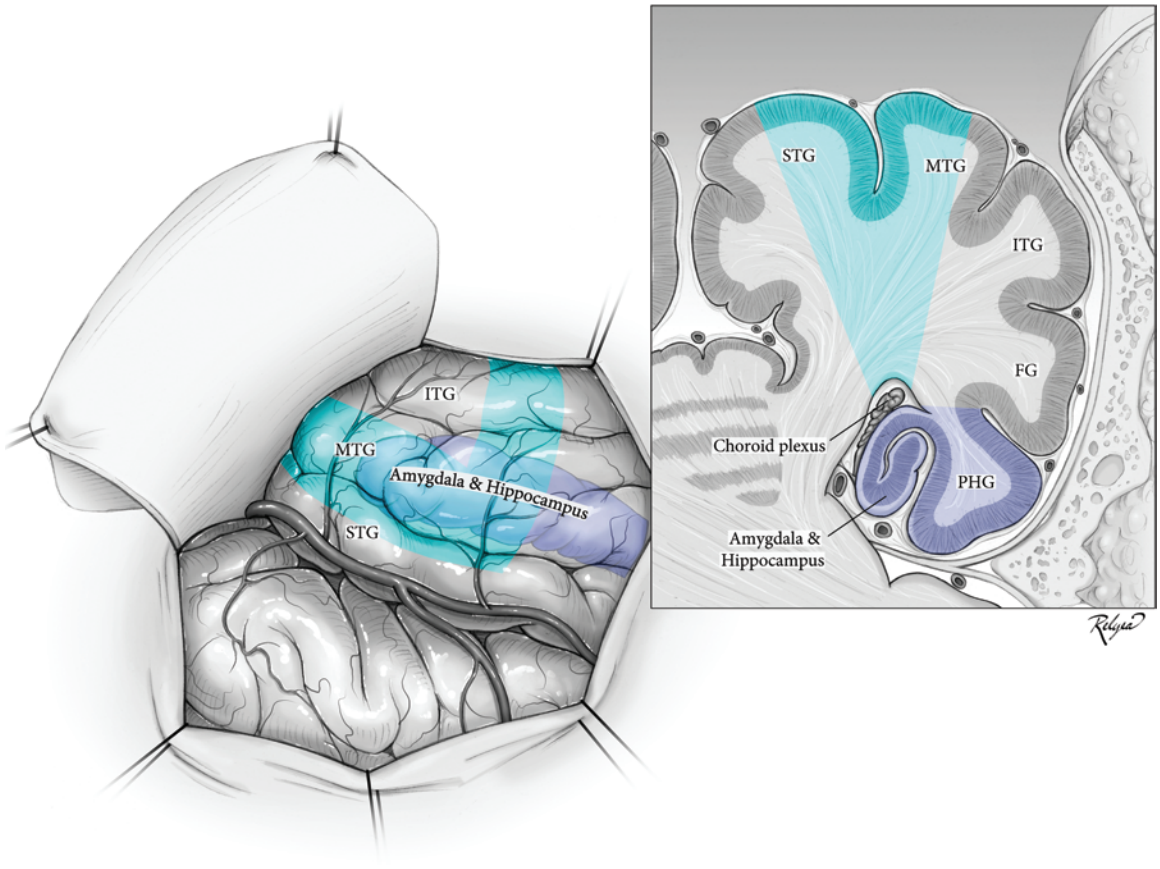

Fig. 2. Artist's illustration of the anterior temporal lobectomy. The incision is made through the superior temporal gyrus (STG) or middle temporal gyrus (MTG) 4–4.5 cm from the temporal tip angling caudally and slightly posteriorly until the temporal horn is reached. The lateral neocortex is released by completing the resection orthogonally to the middle temporal fossa; next the hippocampus, parahippocampal gyri (PHG), and amygdala are resected. FG = fusiform gyrus; ITG = inferior temporal gyrus.

lateral ventricle (Fig. 3D–F and H). The amygdala and hippocampus are then resected in the same manner as described above (Fig. 3G and I).

Transcircular Sulcus Exposure of the Ventricular Atrium

After removing the mesial temporal lobe structures, the atrium is identified. The dissection continues with the removal of the operculum of the supramarginal gyrus overlying the atrium of the lateral ventricle to expose the atrium. Branches of the middle cerebral artery that supply the parietooccipital area and large veins should be preserved to minimize cerebral edema or infarcts. Partial resection of the supramarginal gyrus may assist in exposure of the atrium (Fig. 4A–D). After the hippocampal structures have been resected, the free edge of the tentorium is followed posteriorly until its junction with the falx (Fig. 4E and F). As the tentorium ascends, several structures are identified: the tail of the hippocampus, the crus fornicis, the calcar avis and bulb of the callosum (medial wall of the atrium), precuneus, and the cuneus. These structures should be disconnected behind the choroid plexus of the atrium. The medial wall of the atrium is disconnected by following the free edge of the tentorium up to the roof of the atrium, which is formed by the splenium of the corpus callosum. This disconnection can be confirmed using neuronavigation.

Internal Capsule Transection Under the Central Sulcus

The pia-arachnoid and cortex of the frontoparietal operculum is incised 1.5–2 cm above the sylvian fissure. The goal is to enter into the lateral ventricle perpendicularly, ideally above the caudate nucleus (Fig. 5A). At this point neuronavigation is useful to confirm the appropriate entrance into the ventricle (Fig. 5B). Conversely, the frontal and parietal opercula can be resected to lessen the need for retraction. Using a subpial dissection technique, the cortex and white matter are resected until the circular sulcus surrounding the insular cortex is exposed (Fig. 5C). Once the ventricle is entered, large cottonoids are placed in the ventricle to avoid blood entrance into the ventricle. This suprasylvian window is extended from the anterior-most aspect of the superior circular sulcus to its most posterior aspect at the level of the ventricle trigone. The cortisectomy should complete a C-shaped disconnection by joining with the prior incision of the posterior circular sulcus (Fig. 5D–F).

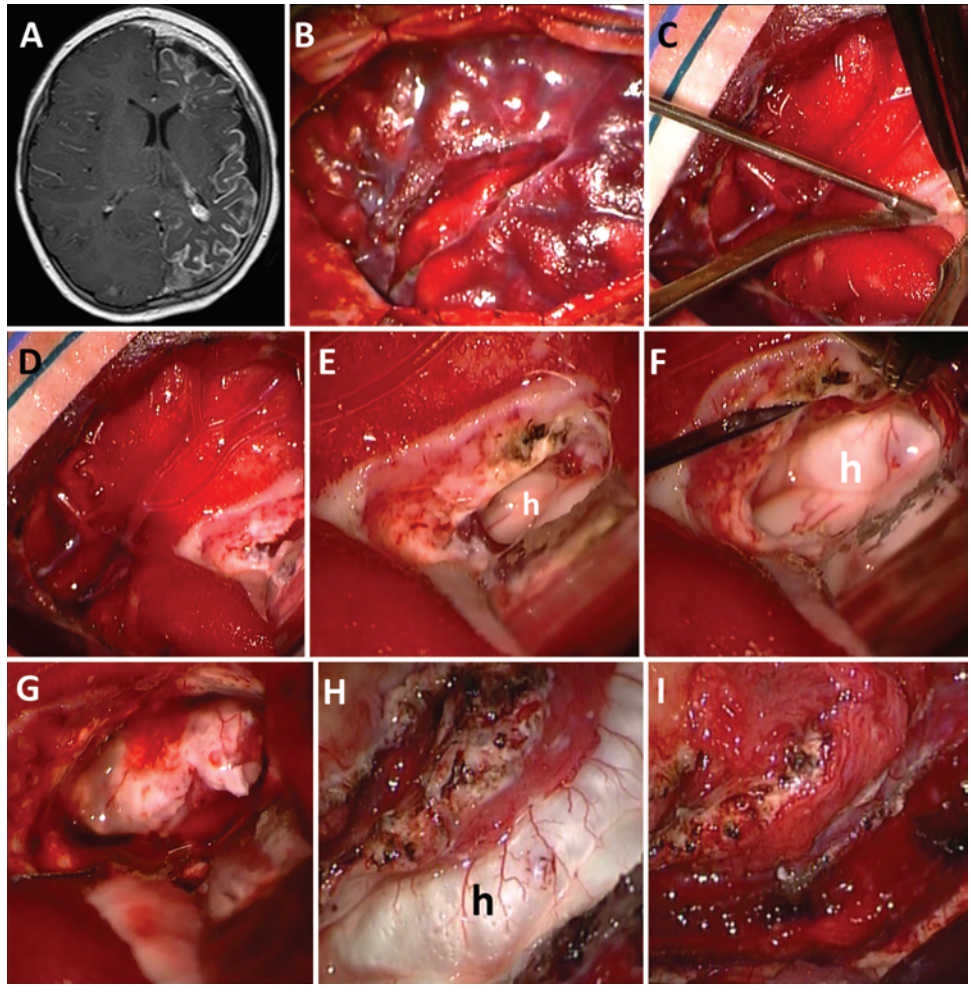

Fig. 3. Transsylvian amygdalohippocampectomy. **A:** Axial T1-weighted MRI of the brain with contrast administration in a 3-year-old child with Sturge-Weber syndrome and intractable epilepsy. **B–G:** Intraoperative images of the patient with Sturge-Weber syndrome (notice the hyperemic appearance of the cortex) undergoing transsylvian amygdalohippocampectomy. **B:** The lateral aspect of the frontal and parietal lobes and the temporal lobes have been exposed. The superficial portion of the sylvian fissure has been dissected. **C and D:** Dissecting through the white matter of the temporal stem into the temporal horn of the lateral ventricle. **E and F:** The temporal horn has been opened and the hippocampus *(h)* is seen. **G:** The head and body of the hippocampus have been resected. **H and I:** Intraoperative images from a different patient before (H) and after (I) the hippocampal resection.

Intraventricular Callosotomy

Once the internal capsule transection has been completed, the medial disconnection can be initiated (Fig. 6). Medial landmarks include the septum pellucidum and the lateral ventricle. The slight angle formed by the junction of the corpus callosum and the septum pellucidum is identified and can be used to mark the site of the callosotomy (Fig. 6A and B). Typically the intraventricular corpus callosotomy is performed 3 mm off midline. By initiating the callosotomy with a small (2–3 mm) vertical incision in the superomedial aspect of the ventricular roof, the pericallosal arteries can be delineated. Once the pericallosal artery is identified (Fig. 6E), the ependyma of the ventricular roof is incised and the callosotomy is extended 1 cm at a time to follow the course of the artery. Preoperative T2-weighted coronal MRI is very useful for studying the relationship between the ipsilateral and contralateral pericallosal arteries and the corpus callosum, allowing the surgeon to predict arterial course changes and ensure that only the ipsilateral pericallosal artery is followed. The pericallosal artery is followed posteriorly to connect to the previously made incision in the splenium and anteriorly through the body, genu, and rostrum of the corpus callosum (Fig. 6).

Frontobasal Disconnection

After the intraventricular callosotomy is completed and after the rostrum of the corpus callosum is disconnected (which corresponds to the floor of the anterior horn), the most anterior portion of the interhemispheric fissure is identified. This can be accomplished by identifying the anterior cerebral artery or the anterior communicating artery. The disconnection continues anteriorly to the head of the caudate nucleus and inferiorly through the basal part of the frontal lobe. The edge of the sphenoid wing is identified and used as a landmark to indicate the

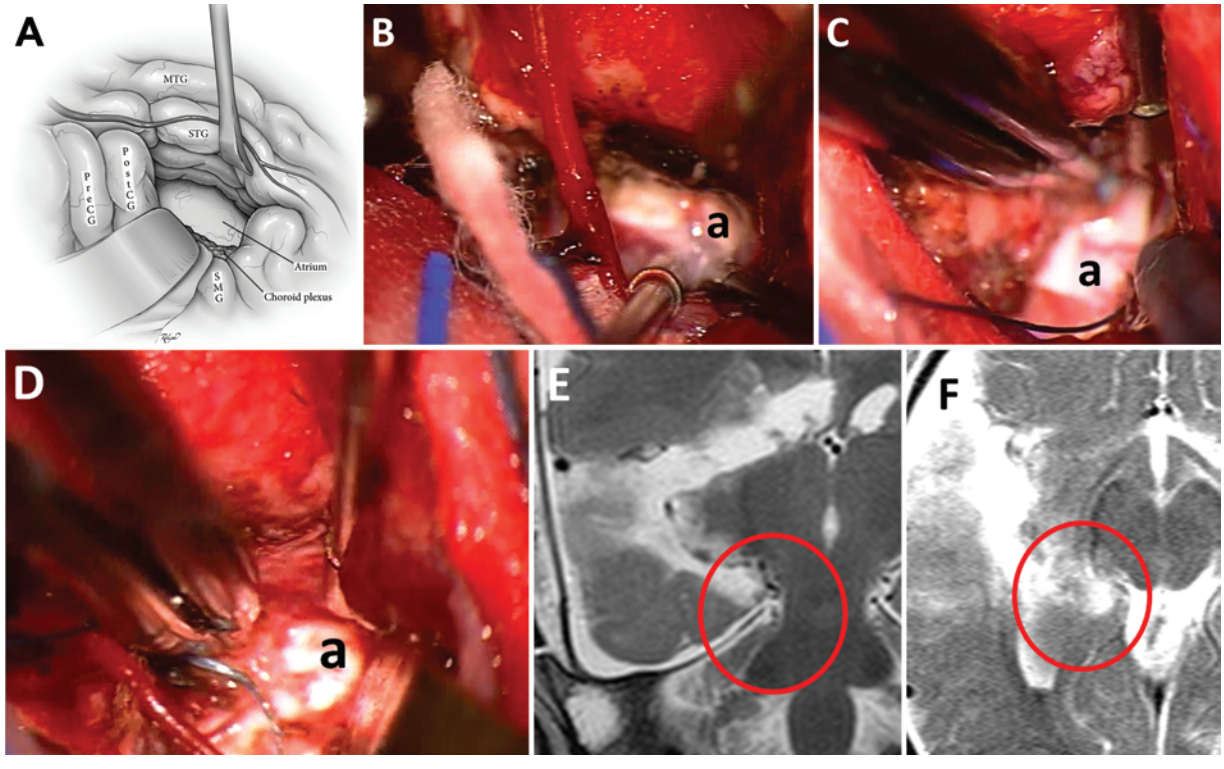

Fig. 4. Transcircular sulcus exposure of the ventricular atrium. **A:** Artist's illustration showing the exposure of the atrium. SMG = supramarginal gyrus; PreCG = precentral gyrus; PostCG = postcentral gyrus. **B–D:** Intraoperative images showing the entrance into the atrium *(a)* using the previously exposed posterior temporal horn. A branch of the middle cerebral artery was preserved (B). **E and F:** Postoperative MRI showing the resection of the entire hippocampus until the free edge of the tentorium is reached. *Circle* indicates termination of the hippocampal resection (junction of the tentorium and the falx).

posterior limit of the basal surface of the frontal lobe. A 5-mm–wide frontobasal gray and white matter subpial aspiration allows for visualization of the olfactory tract and optic nerve through the pia. The optic nerve, internal carotid artery, and proximal anterior and middle cerebral arteries may be injured at the lateral end of the frontobasal disconnection. It is important to maintain a pial boundary during this step to avoid these complications (Fig. 7).

Aspiration of the Insular Cortex

The last stage of the periinsular hemispherotomy is the aspiration of the insular cortex. Due to the anatomical distortion from periinsular dissection, the resection of the insula should systematically resect 3 short gyri and 2 long gyri to ensure complete removal of insular tissue.

Discussion

The physiological goal of a functional hemispherectomy is to isolate the epileptogenic zone from the contralateral healthy hemisphere. Clinically, the objectives in children are to control seizures, prevent cognitive decline, and improve behavioral disorders.[6,8] In children, several age-related considerations exist that may influence the surgical indications. Perioperative death is related to age due to relatively small blood volumes and cerebral malformations that require larger resections. However, surgical intervention at a young age also confers advantages of neural plasticity in which the brain is capable of transferring partial motor function and language capability to the nondominant hemisphere. The overall outcomes among the different techniques do not differ significantly—functional hemispherectomy, vertical, and lateral hemispherotomy have similar results. Typically complete seizure control is observed in 70%–90% of patients regardless of the type of procedure.[3,5,7,9,10,20,24,25]

Functional Anatomical Disconnection of the Periinsular Hemispherotomy

The initial part of the disconnection starts with the mesial temporal structures. There are 4 potential epileptogenic structures with efferent connections: 1) the anterior temporal cortex and paralimbic gyrus via the anterior commissure; 2) the hippocampus via the fimbria-fornix; 3) the amygdala complex via the stria terminalis and projections to the basal ganglia, thalamus, hypothalamus, and brainstem; and 4) the insular cortex via projections to the basal frontal lobe, basal ganglia, thalamus, hypothalamus, and brainstem. Due to the complex continuity of the amygdala and basal ganglia, its resection is mandatory and should be more aggressive. After the neocortical resection of the anterior temporal lobe, the only efferent fibers from the hippocampus are via the fimbria-fornix, and these are sectioned at the level of the atrium. The importance of resection of the insula is debatable and its removal was not found to result in higher seizure control, although resection in the setting of Rasmussen enceph-

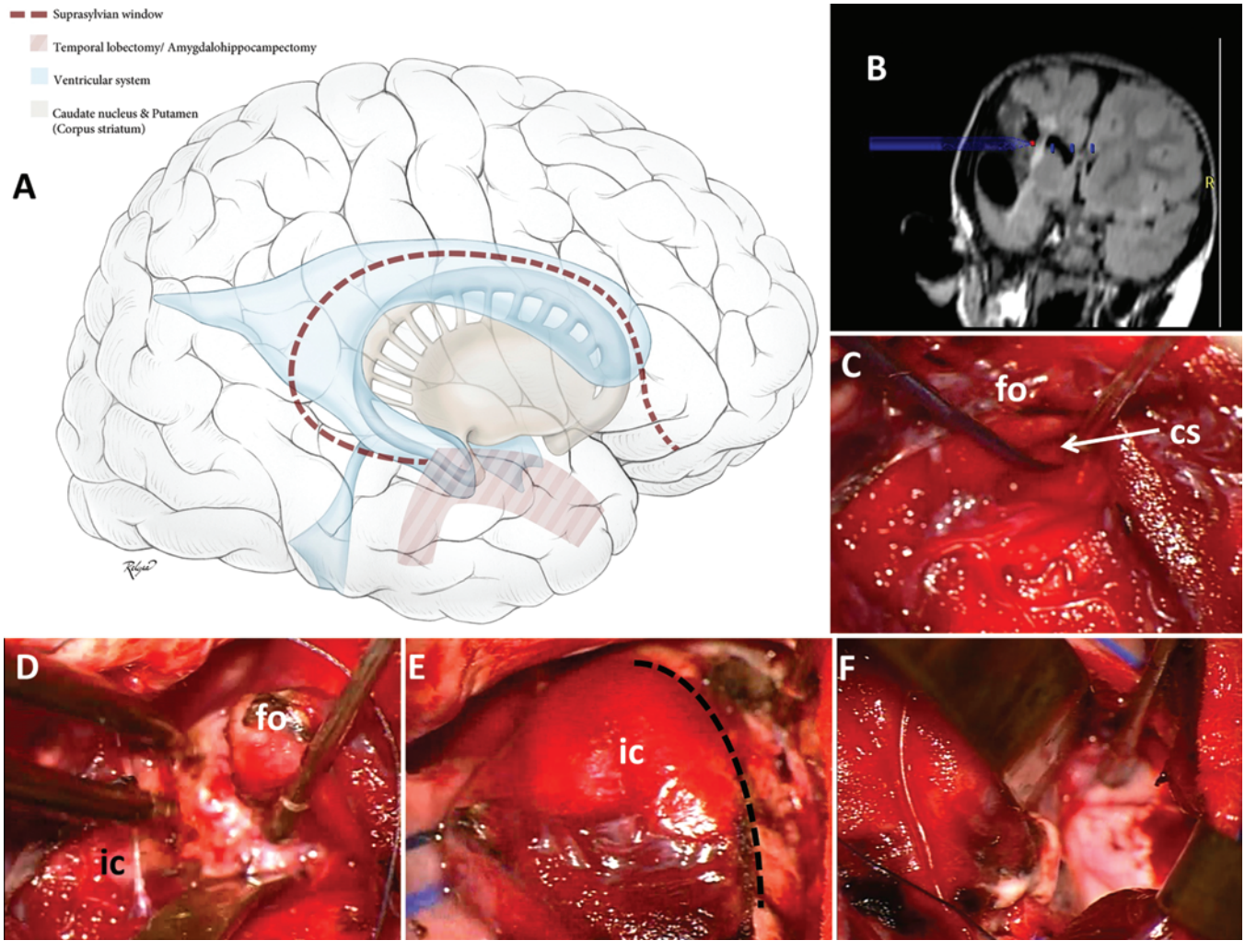

Fig. 5. Internal capsule transection under the central sulcus. **A:** Artist's illustration showing the incision through the entire internal capsule along the lateral ventricle, ideally above the head of the caudate nucleus. **B:** Coronal neuronavigation image confirming the entrance into the lateral ventricle at the desired site. **C:** The frontal operculum *(fo)* is retracted exposing the superior limb of the circular sulcus *(cs)*. **D and E:** The white matter is resected around the insular cortex *(ic)* until the circular sulcus is exposed. The *dashed line* (E) indicates the edge of the insular cortex. **F:** The lateral ventricle has been entered.

alitis may be worth the extra operating time and blood loss.[24] By opening the rest of the temporal horn posteriorly to the atrium, the sublentiform and retrolentiform components of the internal capsule are sectioned. The incision along the circular sulcus toward the lateral ventricle disconnects descending and ascending fibers of the internal capsule at the level of the corona radiata. The frontoparietal commissural connections are disrupted with a parasagittal intraventricular callosotomy that extends anteriorly to the rostrum of the corpus callosum. At this point the most rostral part of the anterior commissure is still intact. The frontal lobe still has some connections: 1) bifrontal caudal orbitofrontal cortices via the anterior commissure (anterior bundle); 2) projections of the frontobasal cortex via anterior sublenticular fibers; 3) cortical connections between orbitofrontal and insular cortices; 4) uncinate fasciculus; and 5) arcuate fibers (parietooccipital fibers). The frontobasal disconnection disrupts the connections described above.

Advantages of Periinsular Hemispherotomy

The original anatomical hemispherectomy has undergone several modifications to avoid late complications. One of the main complications that typically led to death was superficial cerebral hemosiderosis. This complication appeared to be related to size of the postsurgical cavity, where multiple hemorrhages and subdural membranes tend to occur.[14,24] All the most recent functional hemispherotomy techniques have the reduction of this cavity in common. Periinsular hemispherotomy leaves a large amount of viable nonfunctional hemisphere. Anatomical hemispherectomy and hemidecortication typically require a large skin and bone flap, usually reaching the midline. This type of craniotomy is related to blood loss and its complications (hypovolemia and coagulopathies), especially given the blood volume in young children.[2] The small craniotomy required for periinsular hemispherectomy decreases blood loss and operative

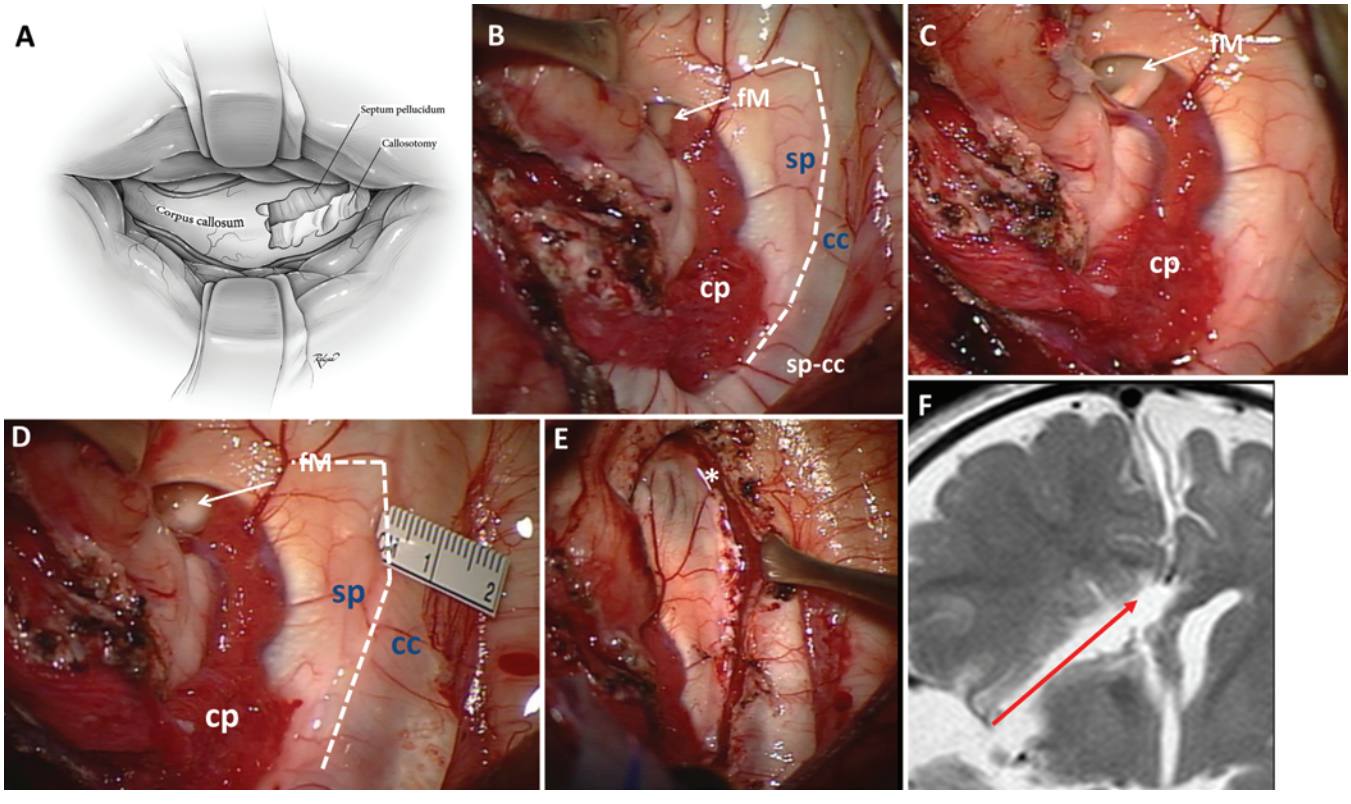

Fig. 6. Intraventricular callosotomy. **A:** Artist's illustration showing the intraventricular view of the corpus callosum. The incision is ideally performed at the union of the septum pellucidum *(sp)* and the corpus callosum *(cc)*. **B:** Intraoperative image showing an overview of the entire lateral ventricle, demonstrating the choroid plexus *(cp)*, the foramen of Monro *(fM)*, and the septum pellucidum-corpus callosum *(sp-cc)* union *(dashed line)*. Notice the grayish appearance of the corpus callosum compared with the septum pellucidum. **C:** Close-up of the foramen of Monro. **D:** Typically the sp-cc junction is 2 cm from the beginning of the corpus callosum; however, this is variable depending on the patient's age. **E:** The pericallosal artery *(asterisk)* is used as a reference to continue the callosotomy. **F:** Postoperative T2-weighted coronal MRI showing the trajectory *(arrow)* of the transection of the internal capsule and the corpus callosotomy.

time. Another early or late complication of anatomical hemispherectomy is hydrocephalus, occurring in as many as 50% of the patients, which is related to the elimination of subarachnoid space over the operated convexity.[7,12,23] Periinsular hemispherotomy spares a substantial amount of subarachnoid space, significantly decreasing the incidence of hydrocephalus.

Disadvantages of Periinsular Hemispherotomy

Disadvantages related to the periinsular hemispherectomy come from difficult anatomical orientation, postoperative brain swelling, and transventricular tissue manipulation. Incomplete disconnection is a significant risk; it has been observed to be a risk with all types of functional hemispherectomies.[16,19] Early postoperative MRI is useful for demonstrating adequate disconnection (Fig. 8); it shows a layer of blood reaching the mesial or basal arachnoid membrane as a sign of complete disconnection.[21] Early hydrocephalus is noted in 5%–64% in all types of functional hemispherectomy[21,22] Death related to a functional hemispherectomy is very rare; a death related to the procedure was reported,[21] but in that case other factors might have contributed, such as aspiration due to mental obtundation secondary to brain swelling. In patients with hemimegalencephaly, we advocate a certain degree of brain resection to allow space for postoperative swelling, temporal lobectomy, or resection of the insular or frontal operculum.

Other Types of Functional Hemispherectomy

Other types of functional hemispherectomy or hemispherotomy use partial resection and hemisphere disconnection and use callosotomy and disconnection of the frontal and occipital lobes. The Rasmussen type involved a resection of the temporal lobe and central part of the frontal and parietal lobe, approximately the length of the corpus callosum, and a subpial disconnection of the frontal and occipital lobe. The vertical approach described by Delalande et al.[5] begins with a parasagittal parietal corticectomy down to the lateral ventricle. The corpus callosum is then identified, the roof of the lateral ventricle followed, and its fibers disconnected. Next, the temporal horn is reached through the corona radiata, and the medial temporal structures and the frontal and occipital lobes are disconnected. Recently, Schramm and colleagues[21] modified the original technique and used the transsylvian keyhole functional hemispherectomy. Shimizu and Maehara[22] also modified the original technique with a modified periinsular hemispherotomy. They proposed a superior window between the inferior frontal gyrus and

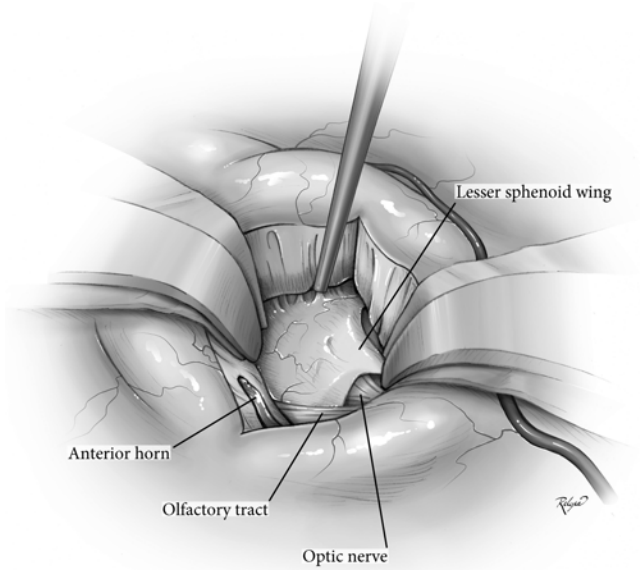

Fig. 7. Artist's illustration showing the frontobasal disconnection. Once the corpus callosotomy has been completed, the final resection proceeds from the most anterior part of the anterior horn down to the sphenoid wing ridge. Usually the olfactory nerve and in some cases the optic nerve can be seen.

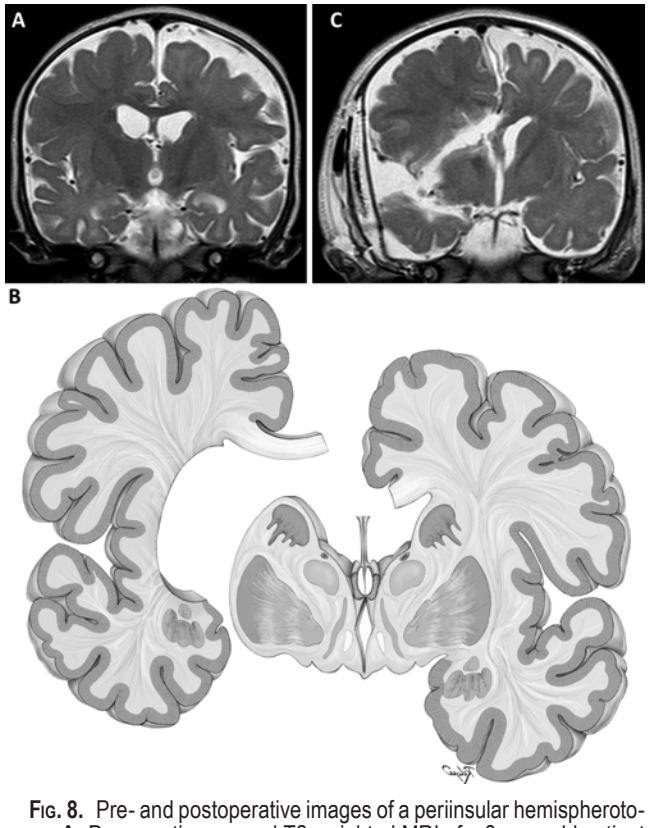

Fig. 8. Pre- and postoperative images of a periinsular hemispherotomy. **A:** Preoperative coronal T2-weighted MRI of a 3-year-old patient with hemimegalencephaly and intractable epilepsy. **B:** Artist's illustration showing a coronal view of the periinsular hemispherotomy. **C:** Postoperative coronal T2-weighted MRI demonstrating the periinsular disconnections.

the superior part of the insula, and through this space, the medial cerebral arteries are coagulated, the mesial temporal structures are resected, and the rest of the hemisphere disconnected. Recently, Bahuleyan et al.,[1] in a cadaver study, demonstrated the feasibility of a minimally invasive endoscopic transventricular hemispherotomy using only 2 bur holes. However, this technique has not been applied to humans.

Conclusions

Periinsular hemispherotomy is an effective procedure that allows complete disconnection and isolation of the diseased hemisphere with a minimal amount of brain resection. Complications from an anatomical hemispherectomy, such as superficial cerebral siderosis and hydrocephalus, are less frequent.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Rangel-Castilla, Hwang. Acquisition of data: Rangel-Castilla, Hwang, Al-Shamy, Curry. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: Jea, Curry. Study supervision: Curry.

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Seizure outcomes and mesial resection volumes following selective amygdalohippocampectomy and temporal lobectomy

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Object. Anterior temporal lobectomy (ATL) and selective amygdalohippocampectomy (SelAH) are the preferred surgical approaches for the treatment of medically refractory epilepsy involving the nondominant and dominant temporal lobes, respectively. Both techniques provide access to mesial structures—with the ATL providing a wider surgical corridor than SelAH. Because the extent of mesial temporal resection potentially impacts seizure outcome, the authors examined mesial resection volumes, seizure outcomes, and neuropsychiatric test scores in patients undergoing either ATL or transcortical SelAH at a single institution.

Methods. A retrospective study was conducted in 96 patients with medically refractory mesial temporal lobe epilepsy. Fifty-one patients who had nondominant temporal lobe epilepsy underwent standard ATL, and 45 patients with language-dominant temporal lobe epilepsy underwent transcortical SelAH. Volumetric MRI analysis was used to quantify the mesial resection in both groups. In addition, the authors examined seizure outcomes and the change in neuropsychiatric test scores.

Results. Seizure-free outcome in the entire patient cohort was 94% at a mean follow-up of 44 months. There was no significant difference in the seizure outcome between the 2 groups. The extent of resection of the mesial structures following ATL was slightly higher than for SelAH (98% vs 91%, $p < 0.0001$). The change in neuropsychiatric test scores largely reflected the side of surgery, but overall IQ and memory function did not change significantly in either group.

Conclusions. Transcortical SelAH provides adequate access to the mesial structures, and allows for a resection that is nearly as extensive as that achieved with standard ATL. Seizure outcomes and neuropsychiatric sequelae are similar in both procedures.

(http://thejns.org/doi/abs/10.3171/2011.12.FOCUS11342)

Key Words • epilepsy surgery • temporal lobe • anterior temporal lobectomy • amygdala • hippocampus • entorhinal cortex

The treatment of medically refractory mesial temporal lobe epilepsy is predominantly surgical, and the results of the ATL have been well described.[5,6,14,16,22] Seizure-free outcomes usually fall in the range of 60%–70%, although higher outcomes have been reported.[12,15,19] The extent of mesial resection necessary for optimal seizure outcome following ATL has been investigated in a number of studies. In 1984, a study published by Spencer et al.[17] suggested that 20% of patients undergoing ATL have the primary epileptogenic focus within the posterior hippocampus. This has prompted some to suggest that postoperative seizure outcome may be improved with a more complete hippocampal resection. A prospective, blinded study in which 70 patients were randomized into 2 groups differing in the extent of hippocampal resection showed that patients undergoing complete hippocampal resections had better postoperative seizure outcomes than those undergoing conservative resections (69% vs 38% seizure free at 1 year).[24] This study and other retrospective series have suggested that, when it comes to hippocampal resection, more is better.[2,9]

Whereas a radical excision of the hippocampus is not typically problematic in nondominant temporal lobe

Abbreviations used in this paper: ATL = anterior temporal lobectomy; BNT = Boston Naming Test; FSIQ = full-scale IQ; MMSE = Mini-Mental State Examination; PIQ = performance IQ; PM = pictorial memory; SelAH = selective amygdalohippocampectomy; VIQ = verbal IQ; VM = verbal memory.

surgery, resections in the language-dominant hemisphere are influenced by the presence of important language-bearing regions within the temporal neocortex. Broad neocortical resection is therefore not usually advocated unless the regions resected are devoid of language function. This approach has led some to advocate resections either guided by intraoperative stimulation mapping or extraoperative mapping with subdural grids. Although either of these approaches allows for broad exposure of the mesial temporal lobe, the former involves a lengthy and somewhat stressful operation, and the latter requires 2 separate operations and a lengthy hospital stay. Maximal neocortical exposure therefore involves added risk, patient inconvenience, and costs.

Other surgical techniques used in dominant temporal lobe resection take a less radical approach. The superior temporal gyrus–sparing temporal lobectomy, for example, is based on the assumption that most temporal lobe language areas reside in the superior temporal gyrus.[18] This approach affords extensive mesial exposure with a lower risk of postoperative language deficit. A more minimally invasive surgical technique is the SelAH. Pioneered by Niemeyer[10] in the 1950s, and Wieser and Yaşargil[23] in the 1970s, SelAH minimizes lateral temporal injury during removal of the mesial structures. Yaşargil's original approach involved a transsylvian exposure, which involves fairly extensive dissection of the middle cerebral artery branches.[26] The risks of vascular injury and retraction injury have been blamed in the reports of stroke and language deficit associated with this technique.[1,28] With the advent of image guidance surgery, a transcortical SelAH involving a corticotomy of the middle temporal gyrus has offered a safer approach to the mesial structures.[11,21] Finally, a subtemporal SelAH has been described, which further reduces the risk of temporal lobe intrusion while minimizing the risk to the middle cerebral artery.[7]

The various merits and disadvantages of these approaches have been argued in the literature, but comparisons have been difficult due to the lack of data from randomized studies. Still, the overarching concern regarding minimally invasive approaches has centered on the reduced access corridor to the mesial temporal lobe, which could theoretically impact seizure outcome.[13,17,24] Several groups have nevertheless examined the seizure outcomes following SelAH, and have reported outcomes on par with standard anteromesial resections reported in the literature.[3,12,19] However, there is as of yet no direct comparison of mesial resection volumes between SelAH and standard ATL. We set out to determine whether there is a difference in the extent of mesial resection between SelAH and standard ATL in a single institution, and whether there are any differences in seizure outcomes or in neuropsychological outcome.

Methods

Patient Population

We retrospectively identified all patients who underwent temporal lobe resections for mesial temporal epilepsy at the University of Michigan between 2001 and 2007. All patients underwent an extensive presurgical workup that included interictal electroencephalographic recordings, neuropsychological evaluation, and speech and language testing, as well as video electroencephalographic monitoring, imaging studies, and intracarotid methohexital testing (Wada test). During this time period, all nondominant resections consisted of a standard ATL, according to techniques described elsewhere.[17,18] Resections of the mesial temporal structures in the language-bearing hemisphere were all performed using an image-guided, transcortical SelAH, according to established techniques.[11,25,27] All operations were performed by a single surgeon (O.S.). Patients with pathological entities suspected outside the mesial temporal lobe were excluded from the analysis. Outpatient clinic notes from both neurosurgical and neuroepilepsy follow-up visits were reviewed. Demographic data, duration of epilepsy, side of surgery, surgical technique, use of invasive monitoring, and pathological entity were recorded.

We examined the seizure outcomes of these patients according to the Engel Classification (Table 1) at various follow-up intervals.[4] At each point, we considered the occurrence of seizures in the prior 1-year period when determining the seizure outcome class (unless less than 1 year had elapsed since surgery at that point). In addition, the volumes of resected tissue in the mesial temporal lobe were determined in the regions of the amygdala, hippocampus, and entorhinal cortex (see below). Finally, neuropsychological test data (VIQ, PIQ, FSIQ, BNT, VM, PM, and MMSE) in these patients were analyzed preoperatively and again 3 months postsurgery. A minimum of 1 year of follow-up seizure data were available for all patients included in the analysis. Patients with shorter follow-ups were excluded.

Volumetric Analysis With MRI

Volumetric MRIs were acquired using a 1.5-T scanner (GE Healthcare or Phillips Medical Systems). High-resolution spoiled gradient–recalled acquisition sequences were acquired using a head coil at 1.5- to 1.7-mm-thick slices with no interslice gap. Preoperative and postoperative residual volumetric measurements following temporal lobe surgery were obtained in the following manner: a single operator (J.P.T.) performed manual tracings around respective mesial temporal structures as viewed on coronal slices to form 2D areas. The traced areas of these cross-sections were calculated in square millimeters by our MRI software package (Advantage Windows, AW 4.3; GE Healthcare). Multiplication of the sum of cross-sectional areas by the image slice thickness yielded a volumetric measurement. Subtracting the residual postoperative volumetric measurement from that obtained preoperatively yielded the volume resected; dividing this volume by the preoperative volumetric measurement yielded the extent of resection (Fig. 1). To maintain consistency, volumetric measurements of the amygdala were made caudal to the anterior commissure, and hippocampal measurements were made rostral to the posterior aspect of the collicular plate. Randomly selected studies were analyzed by another author (D.G.H.) for quality assurance. The anatomical guidelines used for the identi-

TABLE 1: Engel classification scheme

Class	Definition
Class I	seizure free*
A	completely seizure free since surgery
B	aura only since surgery
C	some seizures after surgery, but seizure free for at least 2 yrs
D	atypical generalized convulsion w/ antiepileptic drug withdrawal only
Class II	rare seizures ("almost seizure-free")
A	initially seizure free, but has rare seizures now
B	rare seizures since surgery
C	more than rare seizures after surgery, but rare seizures for at least 2 yrs
D	nocturnal seizures only, which cause no disability
Class III	worthwhile improvement
A	worthwhile seizure reduction
B	prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 yrs
Class IV	no worthwhile improvement
A	significant seizure reduction
B	no appreciable change
C	seizures worse

* Excludes early postoperative seizures (first few weeks).

fication of the hippocampus, amygdala, and entorhinal cortex have been previously described.[8,20]

Statistical Analysis

Comparisons of means and calculations of significance were performed using ANOVA through the JMP statistical software package (JMP v.8, SAS Institute). Modeling by generalized estimating equations analysis was performed using STATA v.10 (STATA Corp.). Patient data were clustered according to follow-up, and seizure outcome (family variable) was set as binomial. Correlations were performed in an exchangeable fashion.

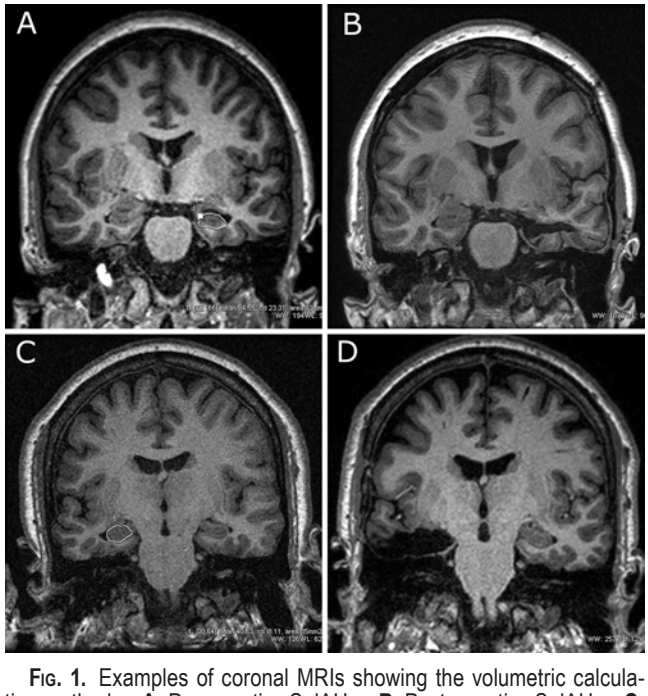

Fig. 1. Examples of coronal MRIs showing the volumetric calculation method. **A:** Preoperative SelAH. **B:** Postoperative SelAH. **C:** Preoperative ATL. **D:** Postoperative ATL. Examples of area tracings outlining the hippocampus are demonstrated on preoperative images. Volumes of mesial temporal structures were calculated based on sequential area tracings and imaging slice thickness.

Results

Patient Characteristics

Between 2001 and 2007, 106 patients underwent temporal lobe surgery for epilepsy. Ten of these patients had follow-up periods of less than 1 year and were excluded from the analysis. Of the remaining 96 patients, 51 underwent ATL and 45 underwent SelAH procedures following presurgical evaluation. Of the patients undergoing ATL, all operations were performed on the nondominant hemisphere (74.5% right; 25.5% left). All patients undergoing SelAH had operations performed on the (language-bearing) left hemisphere. Craniotomy procedures followed by placement of subdural grids and/or depth electrodes were required for initial localization of seizure foci in 35.6% of patients undergoing SelAH and in 17.6% of patients undergoing ATL. The mean duration of follow-up was 43.2 months (ATL group) and 44.7 months (SelAH group). All patients were followed for at least 1 year. Further details are included in Table 2.

Volumetric Analysis

Anterior temporal lobectomy allowed for a near-total resection of the amygdala (99.5%), whereas the extent of resection in SelAH was slightly but significantly lower (93.7%, $p < 0.0001$). Similarly, the extent of resection of

TABLE 2: Characteristics in 96 patients with medically refractory, surgically treated epilepsy*

Characteristic	SelAH	ATL
no. of patients	45	51
mean FU in mos (range)	44.7 (12.3–96.1)	43.2 (13.3–91.5)
sex		
M	20 (44.4%)	26 (51.0%)
F	25 (55.6%)	25 (49.0%)
handedness		
rt	36 (80%)	43 (84.3%)
lt	8 (17.8%)	6 (11.8%)
ambidextrous	1 (2.2%)	2 (3.9%)
epilepsy		
mean age at onset of epilepsy in yrs (range)	17.1 (1–47)	15.0 (1–52)
mean epilepsy duration in yrs (range)	21.2 (1–42)	21.0 (1–57)
w/ secondary generalization	31 (68.9%)	35 (68.6%)
w/o secondary generalization	14 (31.1%)	16 (31.4%)
pathological entity		
MTS	37 (82.2%)	41 (80.4%)
gliosis	8 (17.8%)	0
dysplasia	2 (4.4%)	8 (15.7%)
cavernous malformation	1 (2.2%)	0
hamartoma	0	2 (3.9%)
>1 pathology	3 (6.7%)	4 (7.8%)
op data		
mean age at op in yrs (range)	38.3 (17–57)	36.0 (19–59)
side of op		
rt	0	38 (74.5%)
lt	45 (100%)	13 (25.5%)
w/ grids	16 (35.6%)	9 (17.6%)
w/o grids	29 (64.4%)	42 (82.4%)

* FU = follow-up; MTS = mesial temporal sclerosis.

the hippocampus during ATL was higher than in SelAH (95.8% vs 89.2%, $p < 0.0001$). Finally, resection of the entorhinal cortex was more complete during ATL than for SelAH (100.0% vs 89.8%, $p < 0.0001$). The total mesial resection was therefore more complete in the ATL than in the SelAH group. These differences are illustrated in Fig. 2.

Seizure Outcomes

The ATL Group. Three months after surgery, 47 patients (92.1%) were seizure free (Class I). At 1 year postoperatively, 8 patients (15.7%) who were initially seizure free developed rare seizures (Class II). One patient improved (from Class III to Class II). At 2 years postoperatively, 3 patients improved to Class I and 2 patients worsened; one of these developed rare seizures (Class II) and the other developed seizures with notable worthwhile improvement (Class III). Seven patients were lost to follow-up. Three years after surgery, 85.2% of patients who had undergone ATL were seizure free (Class I). Two patients improved (both Class II; to Class I) and 1 patient developed rare seizures (from Class I to Class II). Seven patients were either lost to follow-up or did not have the requisite follow-up periods. These results are shown in Table 3. At last follow-up, 92.2% of all patients who had undergone ATL had Class I outcomes, with a mean follow-up of 43.2 months (range 13.3–91.5 months). Of the 44 patients with follow-up periods of at least 2 years, 38 were seizure free (Class I) at that point; of these 38 patients, and 37 were seizure free at 1 year.

The SelAH Group. Three months following SelAH, 42 patients (93.3%) were seizure free (Class I). At 1 year postoperatively, 4 patients who were initially seizure free developed rare seizures (Class II), and 1 patient improved from Class III to Class I. At 2 years postoperatively, 4 patients improved to Class I from Class II. Six patients were either lost to follow-up or did not have adequate periods of follow-up. At 3 years postoperatively, 93.1% of patients who had undergone SelAH were seizure free (Class I). Four patients improved to Class I (all from Class II), and 16 patients were unable to meet this period of follow-up. These results are presented in Table 3. At last follow-up, 95.6% of all patients who had undergone SelAH had a Class I outcome, with a mean follow-up of 44.7 months (range 12.3–96.1 months). Of the 39 patients with follow-up periods of at least 2 years, 35 were seizure free (Class I) at that point; of these 35 patients, 32 were seizure free at 1 year.

Factors Predictive of Seizure Outcome

Modeling with generalized estimating equations was used to determine the association of seizure outcome in the Engel class, with several factors as listed in Table 4. Data were clustered according to each patient's progress through his or her own unique period of follow-up, and outcomes were grouped in a binomial fashion—as either Class I (favorable) or non-Class I (unfavorable). Based on

TABLE 3: Seizure outcomes following operation*

Op	Engel Class	No. (%) at FU			
		3 Mos	1 Yr	2 Yrs	3 Yrs
SelAH					
	I	42 (93.3)	38 (84.4)	35 (89.7)	27 (93.1)
	II	2 (4.4)	7 (15.6)	4 (10.3)	2 (6.9)
	III	1 (2.2)	0	0	0
	IV	0	0	0	0
total		45	45	39	29
ATL					
	I	47 (92.1)	43 (84.3)	38 (86.4)	23 (85.2)
	II	3 (5.9)	8 (15.7)	5 (11.4)	3 (11.1)
	III	1 (2.0)	0	1 (2.2)	1 (3.7)
	IV	0	0	0	0
total		51	51	44	27

* Data are given as the number of patients grouped by Engel class at points of follow-up.

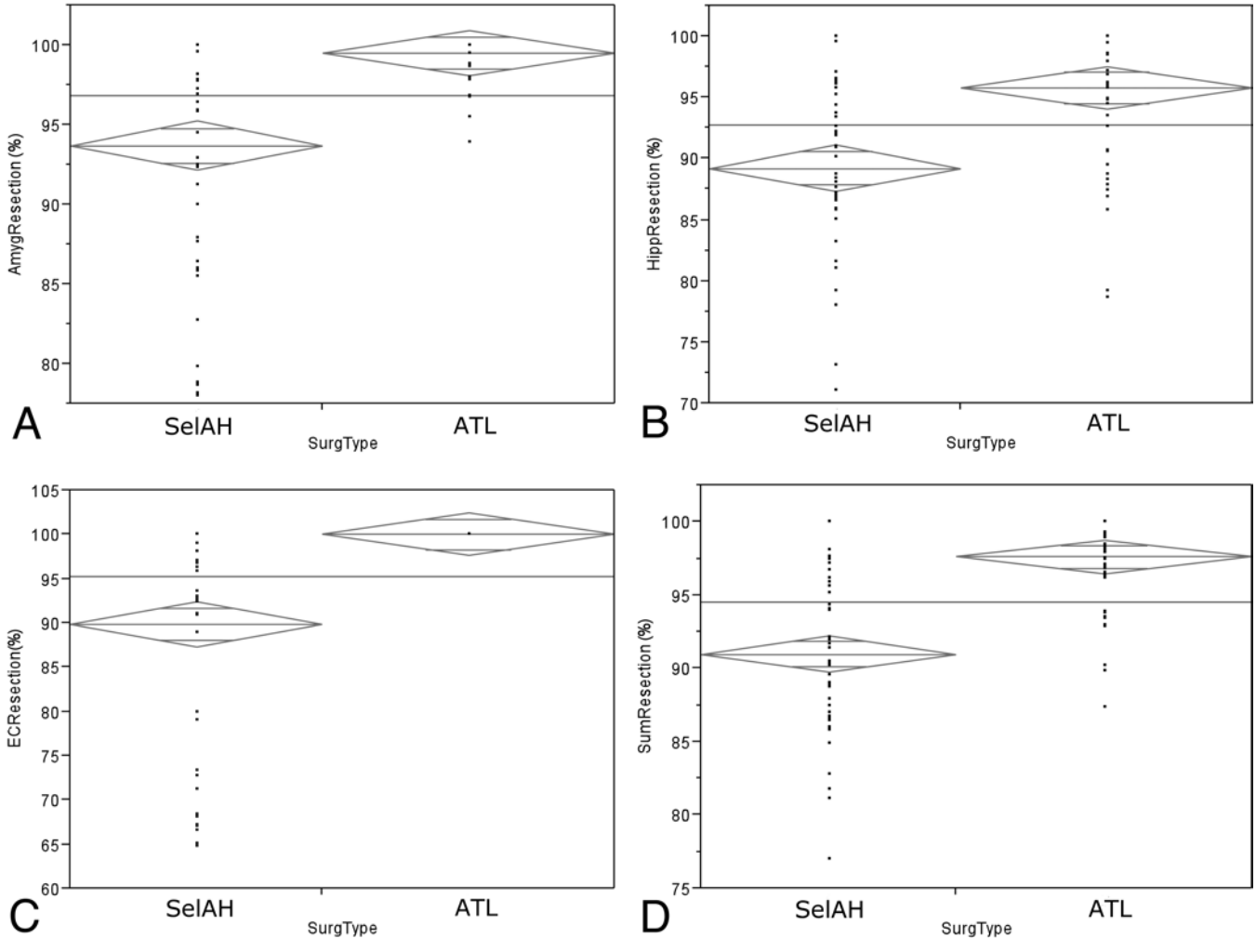

Fig. 2. Graphs showing comparisons of percent resection, grouped by operation type. **A:** Amygdala (Amyg). **B:** Hippocampus (Hipp). **C:** Entorhinal cortex (EC). **D:** Sum of mesial temporal structures. The group mean is reflected in the *horizontal line* across each *means diamond*. Resection volumes were higher in the ATL group in all mesial structures ($p < 0.0001$). The apex and base of each *diamond* delimit the 95% confidence interval. The mean of the entire patient population is shown in the *horizontal line* across the whole graph.

the generated model, the implantation of grids and/or depth electrodes was shown to be weakly associated with unfavorable seizure outcomes ($p = 0.05$). Notably, the type of operation (SelAH or ATL) and the extent of resection of mesial temporal structures did not correlate with a favorable seizure outcome over time. Sex, patient age at operation, handedness, preoperative secondary generalization, and the duration of a patient's epilepsy similarly do not appear to correlate with seizure outcome over time.

Neuropsychiatric Test Outcomes

The BNT. Expressive language function, as measured by the BNT, did not change significantly with either ATL or SelAH. Preoperative and postoperative BNT scores in patients undergoing ATL differed only slightly (preoperative 49.9, postoperative 49.0 [$p = 0.650$]). Patients undergoing SelAH experienced slightly larger deficits in BNT scores; nevertheless, these changes also failed to achieve statistical significance (preoperative 45.0, postoperative 41.5 [$p = 0.078$]). These results are represented graphically in Fig. 3A.

Intelligence Quotient Testing: VIQ, PIQ, and FSIQ. The VIQ scores remained stable between the preoperative state and the 3-month postoperative evaluation in the SelAH cohort (preoperative 86.1, postoperative 85.5 [$p = 0.825$]). Patients undergoing ATL procedures had a slight increase in VIQ scores, although this too was not statistically significant (preoperative 89.7, postoperative 91.3 [$p = 0.675$]). Both the ATL (preoperative 91.4, postoperative 97.3 [$p = 0.158$]) and SelAH cohorts (preoperative 91.5, postoperative 95.0 [$p = 0.313$]) demonstrated statistically insignificant increases in PIQ scores. Similar increases were demonstrated with FSIQ scores (ATL: preoperative 90.5, postoperative 94.3 [$p = 0.309$]; SelAH: preoperative 88.3, postoperative 89.4 [$p = 0.682$]). These results are shown in Fig. 3D.

Memory Testing: VM and PM. Patients undergoing SelAH experienced a statistically significant decrease in

TABLE 4: Generalized estimating equations modeling of parameters having a possible influence on favorable seizure outcome

Parameter	Coefficient	SEM	p Value
type of op (ATL)	0.088	0.071	0.22
age at op	−0.162	0.257	0.53
male sex	0.051	0.053	0.33
rt-handedness	−0.080	0.075	0.28
secondary generalization	0.049	0.058	0.39
age at onset of epilepsy	0.162	0.258	0.53
duration of epilepsy	0.160	0.258	0.53
dual pathology	−0.002	0.100	0.98
grid implantation	0.124	0.064	0.05*
complication	0.028	0.075	0.71
extent of resection			
% sum	−0.032	0.036	0.37
% amygdala	0.018	0.014	0.21
% hippocampus	0.012	0.019	0.52
% entorhinal cortex	0.001	0.005	0.87

* Statistically significant.

VM scores following surgery (preoperative 9.32, postoperative 7.34 [p = 0.013]). The VM scores remained stable in the ATL group (preoperative 12.4, postoperative 12.5 [p = 0.974]). Patients undergoing either procedure experienced no significant change in PM score (ATL: preoperative 8.87, postoperative 8.98 [p = 0.90]; SelAH: preoperative 7.38, postoperative 7.79 [p = 0.658]). These results are illustrated in Fig. 3B.

The MMSE. Overall cognitive performance did not change in patients undergoing either ATL or SelAH. Preoperative and postoperative scores on the MMSE demonstrated no real change in either group (ATL: preoperative 27.0, postoperative 27.5 [p = 0.618]; SelAH: preoperative 26.9, postoperative 26.9 [p = 0.933]). This finding is shown graphically in Fig. 3C.

Discussion

The resection of epileptogenic tissue in the mesial temporal lobe represents the most important factor in the success of temporal lobe surgery. A variety of different approaches have been developed to access these mesial structures in the dominant hemisphere, because language-bearing neocortical regions impede access to this region. Selective resections of the amygdala and hippocampus, via a variety of approaches, minimize the disturbance of temporal language regions. However, the access to the amygdala, hippocampus, and entorhinal cortex is necessarily more limited, and there is a concern that this limitation could lead to incomplete resections and poorer outcome. In this study, we directly compared the extent of mesial resections and seizure outcomes in an institutional cohort, finding that the type of surgical approach influenced neither of these outcomes. Resection of the amygdala, hippocampus, and entorhinal cortex was upward of 90%, regardless of the type of approach. Given this result, the finding that seizure outcomes were not significantly

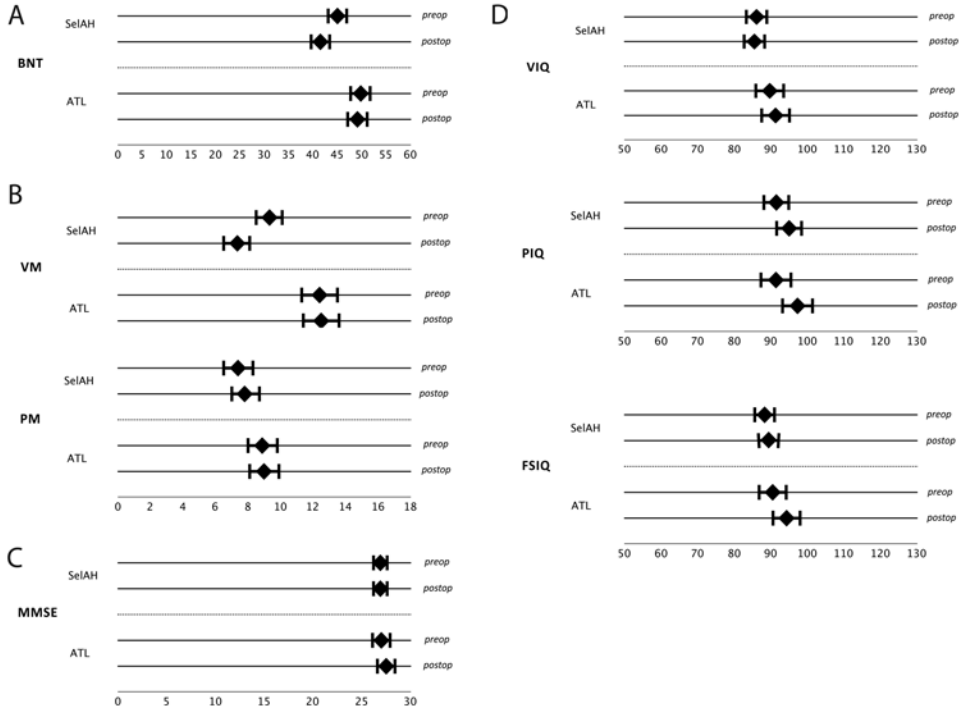

Fig. 3. Graphs showing comparisons of neuropsychiatric parameters grouped by pre- and postoperative values. **A:** The BNT scores. **B:** The memory scores (VM, PM). **C:** The MMSE scores. **D:** The IQ scores (VIQ, PIQ, FSIQ). The error bars delimit the SEM.

different between groups was not surprising. With either ATL or SelAH, 86%–90% of patients were seizure free at 2 years, comparing favorably with the expected range of outcomes reported in the literature.[12,15,19] The early neuropsychological and language sequelae of these surgeries reflected the lateralization of the resection, but in general did not correlate with seizure outcome. The only factor found to correlate with a poor seizure outcome was the use of invasive monitoring (subdural grids or depth electrodes). This is not surprising, since the reason for implantation of these intracranial electrodes was usually related to a question of a second ictal focus.

This study cannot answer the question of whether there is an extent of resection necessary for a good seizure outcome. Because the patients in this study had 90% or more of their mesial structures resected, it would be impossible to determine whether there is a correlation between a less extensive resection and a poorer seizure outcome. Similarly, this study cannot determine whether there is a correlation between specific neuropsychological test score changes and the extent of resection. Finally, we cannot comment on other techniques for SelAH, which use either a transsylvian route or a subtemporal approach. Nevertheless, it does appear that transcortical, image-guided SelAH affords excellent access to the mesial structures and a seizure outcome that is comparable to standard temporal lobe resection. Although these conclusions are limited by the retrospective nature of this study, they do support consideration of selective mesial resection, even in the nondominant temporal lobe.

Conclusions

Selective amygdalohippocampectomy enables the surgeon to remove the amygdala, hippocampus, and entorhinal cortex slightly less completely than is normally achieved using a standard temporal lobectomy. Nevertheless, seizure outcomes and neuropsychological sequelae from the two surgical approaches appear to be comparable.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Sagher. Acquisition of data: Thawani, Gomez-Hassan. Analysis and interpretation of data: all authors. Drafting the article: Sagher, Thawani, Etame. Critically revising the article: Sagher, Etame, Gomez-Hassan. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sagher. Statistical analysis: Thawani. Study supervision: Sagher.

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Failed epilepsy surgery for mesial temporal lobe sclerosis: a review of the pathophysiology

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Object. The object of the current study was to review the electrophysiology and pathological substrate of failed temporal lobe surgery in patients with mesial temporal sclerosis.

Methods. A systematic review of the literature was performed for the years 1999–2010 to assess the cause of failure and to identify potential reoperation candidates.

Results. Repeat electroencephalographic evaluation documenting ipsilateral temporal lobe onset was the most frequent cause for recurrent epileptogenesis, followed by contralateral temporal lobe seizures. Less frequently, surgical failures demonstrated an electroencephalogram that was compatible with extratemporal localization. The generation of occult or new epileptogenic zones as well as residual epileptogenic tissue could explain these findings.

Conclusions. The outcome of temporal lobe surgery for epilepsy is challenged by a somewhat consistent failure rate. Reoperation results in improved seizure control in properly selected patients. A detailed knowledge of the pathophysiology is beneficial for the reevaluation of these patients.
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Key Words • temporal lobe epilepsy • temporal lobectomy • surgical failure • mesial temporal sclerosis

Temporal lobe surgery is an effective treatment for medically resistant mesial TLE. Mesial TLE is characterized by complex partial seizures with typical semiology manifested as epigastric and/or olfactory auras, complex automatisms, loss of awareness, and rarely, generalized convulsive episodes.[48] Epilepsy that is refractory to medical treatment is common, especially if hippocampal sclerosis is present.[26]

The efficacy of temporal lobe surgery to treat refractory epilepsy has been demonstrated in a prospective randomized trial.[53] The "ideal" surgical candidate has mesial TLE with unilateral ictal EEG findings and ipsilateral MRI findings suggestive of MTS. Abnormal signal on FLAIR and T2-weighted imaging, decreased volume, and loss of anatomical configuration of the hippocampal formation are considered the hallmarks of radiographic MTS. The presence of radiographic MTS is considered a predictive factor for favorable seizure outcome after surgical intervention.[2,10,22,39] Temporal lobe resection has reported success rates ranging from 70% to 90%.[8,24,44,45] Certainly, the existence of preoperative bilateral MTS or extrahippocampal pathology is associated with a greater likelihood of seizure recurrence, and as a result, this group of patients will not achieve the same degree of seizure control as patients with unilateral disease.

McIntosh et al.[32] performed a systematic review of results for temporal lobe surgery for epilepsy. The authors reported that the proportion of patients with documented seizure-free outcome varied widely between 33% and 93% (median 70%). They identified multiple issues when gathering the data, such as differences in definition of outcome, different types of pathology included, and length of follow-up that accounted for the discrepancy in outcome.

Although surgery is considered to be a safe and effective treatment in patients with TLE, the results of this procedure for patients with unilateral MTS are challenged by a somewhat consistent failure rate. The reasons for failure are not well known and there are no data available on the clinical predictors of failed surgery.[1,3,21] Previous studies have demonstrated that late recurrence after initial seizure freedom is not a rare event, but risk factors specific to the event remain elusive. Therefore, the purpose of this study is to discuss the electrophysiology and pathological substrate behind failed temporal lobe resection in patients with unilateral radiographic MTS. This patient population is considered the "ideal" candidate for

Abbreviations used in this paper: EEG = electroencephalography; MTS = mesial temporal sclerosis; TLE = temporal lobe epilepsy.

temporal lobe resection and represents a more homogenous group of patients who are most likely to benefit from surgery and thus represent the best group within which to analyze surgical failures.

Methods

A comprehensive literature review using PubMed was performed. The following search terms were used in multiple combinations: "epilepsy surgery," "temporal lobe," "temporal lobe seizures," "failure," and "outcome." We also searched the bibliographies of review articles, original articles, and book chapters in an attempt to add relevant articles. Literature searches were restricted to English-language full-length articles published between January 1999 and December 2010.

To be considered for this review, patients must have presented with: 1) mesial TLE as characterized by complex partial seizures with the typical clinical semiology of mesial origin (epigastric or psychic auras); 2) video-EEG findings compatible with unilateral ictal temporal lobe onset; 3) high-resolution brain MRI (1.5 T or higher) suggestive of unilateral MTS; 4) a surgical procedure involving either an anterior temporal lobectomy or selective amygdalohippocampectomy; 5) surgical outcome based on Engel classification; 6) at least 1 year of follow-up; and 7) be ≥ 15 years of age at the time of surgery. Because of variation in study design, surgical technique, and outcome reporting, it is difficult to establish the exact proportion of patients who fail to achieve seizure control with surgery. Outcome was defined according to a modified Engel classification:[11] Class I, seizure free with or without residual auras; Class II, rare disabling seizures (> 90% seizure reduction); Class III, < 90% seizure reduction; and Class IV, no worthwhile improvement. Surgical failures were defined as Engel Class III–IV, which included patients with frequent seizures and unsatisfactory outcome. We independently assessed study eligibility and extracted data, resolving disagreements through discussion. The literature search resulted in 651 references, 79 of which were potentially eligible and were selected for full text review. Sixty-five articles were excluded for the following reasons: < 12 months follow-up (3/65, 4.6%), mixed pathology (29/65, 44.6%), absence of hippocampal atrophy on MRI (20/65, 30.8%), pediatric patients < 15 years of age included in series (2/65, 3.1%), outcome not determined by Engel classification (2/65, 3.1%), review article (1/65, 1.5%), no analysis of failures (5/65, 4.6%), and study with < 20 patients (3/65, 4.6%). Eight articles were useful for discussion in regards to outcomes and 5 articles were included for analysis of surgical failures.

Results

Five publications[15,17,38,41,43] had enough documentation to assess the causes of failures for this unique population of surgical patients. Only 2 studies[17,38] provided enough information to document incidence of surgical failure in addition to the origin of the problem. Eight studies[7,9,13,23,29,35,38,50] were helpful in documenting the failure rate of temporal lobe surgery in this population (Table 1). Major surgical failures tended to occur early in the follow-up period, usually less than 1 year. Furthermore, the frequency of seizures was significantly lower in patients with late recurrence than in those with an early recurrence of seizures.[9,38] Despite differences in follow-up periods in those studies, the long-term seizure-free rate following resective temporal lobe surgery appears to be similar to that reported in short-term controlled studies.[49]

There were a total of 686 patients identified who met the outcome inclusion criteria. All patients underwent similar mesial temporal lobe resection, but underwent a variable amount of cortical resection based on the descriptions of the surgical technique. However, the surgical approach has not been found to be predictive of outcome.[9,36,46] The incidence of failure was 8.9% (61/686; Table 1). Hardy et al.[16] and Hennessy et al.[17] did not use the Engel classification but documented a failure rate (similar to Engel Class III/IV) of 7.6% and 12%, respectively. Surgical failures (Engel Class III/IV) tended to occur within 1 year. In addition, complete discontinuation of antiepileptic drugs after 2 years has not been associated with an increased rate of recurrence.[10] Fifty-five patients were identified with known electroencephalographic cause for persistent seizures (Table 2). The most common documented reason for failure was persistent unilateral temporal lobe epileptic foci (65%) followed by contralateral seizure onset (29%), and the least frequent cause for recurrent seizures was extratemporal localization (5%).

Discussion

Patients with mesial TLE in the setting of radiographic findings suggestive of unilateral MTS are the ideal candidates for surgical intervention. Medical treatment failures are common, whereas surgery results in seizure control rates of up to 70%–90%.[26,54] Nevertheless, some patients do not have a significant improvement of their condition with surgery, even with complete resection of the suspected epileptogenic zone. Clinical factors such as seizure frequency, duration of epilepsy, sex, age of onset, and laterality of seizure focus have not been shown to

TABLE 1: Literature review of failure rates in patients with unilateral MTS*

Authors & Year	No. of Cases	Engel Class		
		I	II	III/IV
Lowe et al., 2004	48	40	6	2
Dupont et al., 2006	110	78	21	11
Bonilha et al., 2007	43	33	6	4
Georgakoulias et al., 2008	50	37	6	7
Karasu et al., 2008	56	43	10	3
Ozkara et al., 2008	165	129	12	24
Tezer et al., 2008	109	90	17	2
Ramos et al., 2009	105	91	6	8
total (%)	686	541 (78.9)	84 (12.2)	61 (8.9)

* Engel Class III/IV considered a treatment failure.

TABLE 2: Postoperative EEG findings in failed temporal lobe surgery*

Authors & Year	Patients w/ MTS	Surgical Failures (%)	Seizure Type (%)		
			Ipsilat Temporal	Contralat Temporal	Extratemporal
Hennessy et al., 2000	165	20 (12)	12 (60)	6 (30)†	2 (10)
Schwartz & Spencer, 2001	NR	5	4 (80)	1 (20)	0
González-Martínez et al., 2007	NR	10	5 (50)	4 (40)	1 (10)
Salanova et al., 2005	NR	12	10 (83)	2 (17)†	0
Ramos et al., 2009	105	8 (8)	5 (62.5)	3 (37.5)	0
total		55	36 (65)	16 (29)	3 (5)

* Contralat = Contralateral; Ipsilat = Ipsilateral; NR = not reported.

† One patient with bitemporal onset.

be risk factors for postoperative seizure recurrence.[7,25,38] Other authors have identified frequent secondarily generalized seizures,[18,20] history of encephalitis,[41] and head trauma[41,50] as poor predictive factors for good outcome. These findings suggest the presence of a more extensive seizure focus or multifocal epilepsy than what is observed in the typical patient with mesial TLE. In reality, the vast majority of studies have failed to identify factors that are predictive of outcome.[1,14,16,25,33,38,51]

Unfortunately, predictive clinical risk factors have remained elusive. Nevertheless, these patients should not be considered absolute failures of surgical management, instead they should be restudied to determine why surgery failed and to decide if further surgical intervention is indicated. A detailed knowledge of the pathophysiology is required to define potential treatment options.

Reasons for Failure of Temporal Lobe Resection

In general, there are 3 main reasons why epilepsy surgery, regardless of pathology, can fail: incomplete resection of the epileptogenic focus, inaccurate localization and/or mapping of the epileptogenic focus, and the generation of a new epileptogenic focus and/or the emergence of an occult epileptogenic area. To better understand the reasons for failure, attention should be placed on the pathological substrate of this group, which includes residual epileptogenic structures, generation or reactivation of a new epileptogenic focus in the form of contralateral MTS, dual pathology, or possibly, surgical scar. These pathological entities can result in the recurrence of seizures in the temporal or extratemporal cortex. The clinical semiology and electrophysiology of recurrent seizures can then present as ipsilateral temporal, contralateral temporal, or extratemporal seizures.

Ipsilateral Temporal Lobe Seizures. Ipsilateral temporal lobe seizures remain the most common cause of failed surgery (Table 2). Ipsilateral recurrent seizures tend to have both the electrodiagnostic (ictal and interictal epileptiform discharges) and clinical features of temporal lobe semiology. Three pathological conditions could potentially explain surgical failures in this situation: residual mesial structures, dual pathology, and surgical scar.

Residual Mesial Structures. Wyler et al.[55] in a prospective, randomized clinical trial established the superior outcome of temporal lobe surgery associated with aggressive hippocampectomy. Removal of the mesial structures (hippocampus/parahippocampus gyrus) to the level of the superior colliculli allows for better seizure control in patients with TLE. In addition, no increased neuropsychological morbidity was found with more extensive resection of the mesial structures. Since 1995, standardization of the mesial temporal resection has been well established. Hennessy et al.[17] reported 5 of 20 patients and Ramos et al.[38] documented 1 of 8 patients with residual mesial structures and recurrent seizures. They acknowledged that incomplete resection of mesial structures is a potential cause of failure and reoperation might be beneficial in selected patients.

Occult or New Epileptogenic Area. Patients who have adequate resection of the mesial structures and continue to have ipsilateral temporal seizures remain a clinical challenge. Frequently, imaging studies do not reveal any anatomical abnormalities, making it difficult to identify the new epileptogenic zone and therefore plan further treatment. If we come to believe that MTS is the consequence of a more diffuse insult to the brain, it is possible that once the hippocampus is removed other areas of the brain, with a higher seizure threshold and not detected by our current neurophysiology and neuroimaging studies, it can become epileptogenic. Assuming their preoperative imaging was otherwise normal, these patients likely harbor radiographic occult dual pathology. The role of invasive EEG recordings with strips, grids, or depth electrodes in this group is not clear but may be beneficial during the reevaluation phase if further surgery is contemplated.

Dual pathology can take the form of cortical dysplasias, neuronal heterotopias, or migrational disorders and has been the main cause of surgical failures in recent series.[27,28,43] The presence of dual pathology in patients with MTS has been well described in the literature. Some authors have found a 15%–30% incidence of this type of dual pathology in their series of patients with TLE.[27,41] In this situation both the dysplastic temporal neocortex and the sclerotic hippocampus can be epileptogenic. It appears that the contribution of the hippocampus to seizure generation corresponds to the degree of hippocampal pathology, whereas even mild forms of cortical dysplasia can be epileptogenic.[12] This finding has major prognostic implications for patients who undergo selective (limited)

temporal lobe surgery as MRI may not detect mild neuronal and cortical abnormalities that have epileptogenic potential. Li et al.[28] reported a series of patients in whom removal of both the sclerotic mesial structures and extrahippocampal lesions resulted in a 73% seizure-free rate. These are encouraging results but only apply to those patients in which the dual pathology was identified and precisely localized preoperatively.

Surgical Scar. Although the gliotic scar is widely accepted as a cause of epilepsy, there is no direct evidence that scar formation contributes to epileptogenesis. It has been proposed that the meningocerebral scar that forms following trauma to the brain plays an important role in the development of posttraumatic epilepsy. In an animal study[19] epileptogenesis was blocked by procedures that inhibit scar formation. Hennessy et al.[17] stated that epileptogenesis related to a surgical scar was an unlikely explanation for recurrent seizures arising adjacent to the resection. Pathological findings compatible with gliosis at the resection edge may suggest epileptogenic potential. However, surgical scar as a cause of recurrent epilepsy remains a controversial subject.

Contralateral Temporal Lobe Seizures. Limited knowledge of the pathophysiology of MTS has prevented the identification of factors that precipitate neuronal loss and gliosis of the hippocampus. The pathogenesis of mesial TLE is associated with an event that probably injures the hippocampus at some time prior to habitual seizure onset.[31] This event likely affects both hippocampi in an asymmetrical way. Febrile seizures have been recognized as a common offender,[6] but controversy still exists regarding the etiological relationship between MTS and epilepsy. Some investigators view hippocampal sclerosis as the primary cause of TLE, whereas others interpret the changes to be the result of chronic seizure activity.[40] Regardless of the origin, it appears that mesial TLE is a bilateral disease with a broad range of lateralization. Autopsy series corroborate that a high proportion of patients with epilepsy (47%–86% of cases) suffer from bitemporal hippocampal sclerosis.[30,42] Preoperative volumetric MRI studies suggest that most patients with mesial TLE have some degree of bilateral, asymmetrical hippocampal pathology.[5,37] As a result, a high proportion of surgical failures demonstrate contralateral temporal epileptiform activity and in some cases, significant MRI findings to suggest MTS.

Patients with contralateral temporal epileptiform activity are well documented in their respective series of surgical failures by González-Martínez et al.,[15] Hennessy et al.,[17] Ramos et al.,[38] Salanova at al.,[41] and Schwartz and Spencer[43] (Table 2). The events leading to activation of this new epileptogenic area are not understood. Unfortunately, this group of patients is not eligible for further resective surgery as bilateral mesial temporal resections may result in devastating cognitive and behavioral deficits. Further therapeutic options are limited to medical therapy and possible placement of a vagus nerve stimulator.[15,38]

Extratemporal Seizures. Extratemporal seizure origin is not a common cause of failure for patients with MTS (Table 2). The number of documented cases in the literature is scarce.[4] Gonzalez-Martinez et al.[15] reported 1 of 10 patients, and Hennessy et al.[17] documented 2 of 20 patients with extratemporal epileptiform activity in their respective series of surgical failure. For patients with TLE these areas most likely represent dual pathology not diagnosed by the initial neurophysiological and radiographic studies. An extratemporal lesion may cause local epileptiform activity, which then spreads to the hippocampal circuitry, and produces stereotypical complex partial seizures. As a consequence, the hippocampus would then undergo neuronal loss and/or reorganization. In these patients, removal of both the lesion and the atrophic hippocampus should be considered as it provides the best chance for seizure control.[28] To further support this probable scenario, recent evidence suggests that some TLE surgical failures could be related to unrecognized insular epilepsy.[34]

Treatment Options

Based on current experience and available literature, reoperation might be of benefit in selected patients. Further surgical intervention can be considered for those patients with ipsilateral temporal seizures, with or without residual mesial structures, and those with extratemporal seizures if a lesion or epileptogenic cortex can be identified. Results of reoperation are difficult to predict as there are few series published in this particular group of patients. In the study by Gonzalez-Martinez et al.,[15] reoperation consisted of extending the previous resection margin in patients with MTS, which led to good outcomes in only 3 (30%) of 10 patients. However, on further analysis, 4 of these 10 patients were found to have contralateral temporal epileptic activity, explaining their poor outcomes. This finding demonstrates the importance of repeated EEG prior to planning for further resections on surgical failures. Ramos et al.[38] documented 2 of 4 patients who initially had complete resection of the mesial structures and improved to Engel Class I/II with an extended neocortical resection along the basal and lateral cortex of the previous resection cavity. For patients with persistent ipsilateral seizure onset, extension of the cortical resection along the surgical scar appears to be beneficial approximately 50%–60% of the time.[4,14,38,39,41,43] A Phase II evaluation (invasive EEG monitoring with subdural grids/strips/depth electrodes) can be considered prior to further surgical intervention if there are clinical concerns regarding ictal onset localization. Neuropathology correlation with surgically treated TLE patients demonstrates that a subgroup of patients can benefit from more extensive neocortical resection. A significant association between MTS and malformations of cortical development has been found in some patients.[47] Furthermore, Bonilha et al.[7] recently observed that a better surgical outcome was obtained with the removal of the entorhinal cortex in addition to the hippocampus. No pathological correlation was described with their findings, but their conclusion certainly warrants further investigation.

For those patients with contralateral temporal seizures or nonlocalizable seizure onset, a vagus nerve stimulator may be implanted as a last surgical option. There

are no large series reporting the use of a vagus nerve stimulator for failed surgery in MTS cases. Outcome has not improved in the few reported cases.[15,38]

Further understanding of the pathophysiology and mechanisms of epileptogenesis of MTS is necessary before more conclusions are drawn. Whatever the explanation is, it appears that the mechanisms of relapse are heterogeneous. These findings suggest that larger epileptogenic zones exist in these refractory patients. Accurate identification of the epileptogenic area is critical for success. Postsurgery seizure-free outcome should be the goal. Improvement in quality of life may not be observed even in cases in which seizure frequency was greatly reduced. The evolving field of magnetoencephalography and advanced neuroimaging (3-T MRI) may play an essential role in the future for diagnosis of intractable epilepsy, and hopefully allow for a higher rate of seizure-free outcome.[33,52]

Conclusions

Reasons for failure of temporal lobe surgery are multifactorial and clinical predictors are lacking. Ipsilateral recurrent seizures appear to be the most common finding in failed temporal lobe surgery. The generation of new or occult epileptogenic zones in the form of dual pathology or scar tissue is a possible explanation. Incomplete resection of the epileptogenic zones in the form of residual hippocampus is no longer a common cause for surgical failures. Contralateral epileptogenesis also remains a frequent finding. Repeat evaluation is recommended as reoperation results in improved seizure control in properly selected patients. Detailed knowledge of the pathophysiology is beneficial for the treatment of these patients.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Vale, Benbadis. Acquisition of data: Vale, Pollock. Analysis and interpretation of data: Vale, Pollock. Drafting the article: Vale, Pollock. Critically revising the article: Benbadis. Reviewed submitted version of manuscript: Vale. Approved the final version of the manuscript on behalf of all authors: Vale. Study supervision: Vale.

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Long-term outcome of extratemporal resection in posttraumatic epilepsy

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Object. Posttraumatic epilepsy (PTE) is a common cause of medically intractable epilepsy. While much of PTE is extratemporal, little is known about factors associated with good outcomes in extratemporal resections in medically intractable PTE. The authors investigated and characterized the long-term outcome and patient factors associated with outcome in this population.

Methods. A single-institution retrospective query of all epilepsy surgeries at Regional Epilepsy Center at the University of Washington was performed for a 17-year time span with search terms indicative of trauma or brain injury. The query was limited to adult patients who underwent an extratemporal resection (with or without temporal lobectomy), in whom no other cause of epilepsy could be identified, and for whom minimum 1-year follow-up data were available. Surgical outcomes (in terms of seizure reduction) and clinical data were analyzed and compared.

Results. Twenty-one patients met inclusion and exclusion criteria. In long-term follow-up 6 patients (28%) were seizure-free and an additional 6 (28%) had a good outcome of 2 or fewer seizures per year. Another 5 patients (24%) experienced a reduction in seizures, while only 4 (19%) did not attain significant benefit. The presence of focal encephalomalacia on imaging was associated with good or excellent outcomes in 83%. In 8 patients with the combination of encephalomalacia and invasive intracranial EEG, 5 (62.5%) were found to be seizure free. Normal MRI examinations preoperatively were associated with worse outcomes, particularly when combined with multifocal or poorly localized EEG findings. Two patients suffered complications but none were life threatening or disabling.

Conclusions. Many patients with extratemporal PTE can achieve good to excellent seizure control with epilepsy surgery. The risks of complications are acceptably low. Patients with focal encephalomalacia on MRI generally do well. Excellent outcomes can be achieved when extratemporal resection is guided by intracranial EEG electrodes defining the extent of resection.
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Key Words • epilepsy surgery • posttraumatic epilepsy • frontal • magnetic resonance imaging • extratemporal • invasive monitoring

Posttraumatic epilepsy comprises approximately 3–6% of new onset epilepsy cases. As much as 20% of remote symptomatic epilepsy is due to trauma.[11] Posttraumatic epilepsy is the most common cause of remote symptomatic epilepsy in the 15–34-year-old age range, making up approximately 30% of cases.[2,12] The severity of traumatic injury has a correlation with PTE risk: PTE occurs in 40–53% of penetrating head trauma cases and in 5–20% of closed head trauma cases.[13] Recent data indicate that even after mild head injury there is a slight but significant additional risk for epilepsy after several years.[5]

Whereas 30% of epilepsy cases are pharmacoresistent,[18] it is not entirely clear what proportion of patients with PTE develop medically intractable epilepsy. Focal epilepsy is more likely to be pharmacoresistant than generalized epilepsy in adults.[20] The presence of hippocampal sclerosis predicts a higher risk of medical intractability, particularly if it is also associated with another lesion (dual pathology). The location of the cortical epileptogenic zone does not appear be a factor, as there is no difference between temporal lobe epilepsy without hippocampal sclerosis and extratemporal epilepsy in the possibility of achieving seizure control.[20] However, there are some data suggesting that posttraumatic temporal lobe epilepsy (particularly in adult onset and in the absence of mesial-temporal sclerosis) may result in worse outcomes than other types of temporal lobe epilepsy.[19] This difference is presumed to be related to more widespread areas of damage in PTE.

The most commonly identified focus of intractable

Abbreviations used in this paper: EEG = electroencephalography; PTE = posttraumatic epilepsy.

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epilepsy in adults is the mesial temporal lobe. The most common surgery performed is anterior temporal lobectomy/amygdalohippocampectomy with its variations.[15] Whereas the surgical outcomes from temporal lobectomies are very well characterized, there is less published outcome data for extratemporal resections. This is because extratemporal resections for intractable epilepsy are generally performed less commonly, require additional investigation such as invasive monitoring, and are anatomically and etiologically more heterogeneous. Multicenter data from the mid-1990s suggest that less than 25% of epilepsy surgeries are extratemporal resections.[15] Individual centers, however, recently cite higher rates.[1] In particular, there is a paucity of data on extratemporal resections for PTE. A few publications have reported on outcomes that included some posttraumatic extratemporal resections, and have generally noted outcome results, which are summarized in the discussion section.

Furthermore, PTE surgery poses certain diagnostic and treatment challenges that warrant their own discussion. Mainly, due to the presence of scar tissue and adhesions related to the inciting trauma, there is an increased risk for surgical complications. Furthermore, this surgery may involve proximity to eloquent cortical regions that may have altered anatomy due to prior injury. Finally, the localization of the seizure focus may be less clearly defined due to the extent of injury, possible anoxia at the time of injury, and bilateral lesions in the case of coup-counter-coup lesions, as well as by technical issues related to prior craniotomies and breech rhythms. The purpose of this study is to characterize the long-term outcome of extratemporal resections for PTE at the University of Washington.

Methods

Study Population

We performed a retrospective review of patients who underwent operations for medically intractable epilepsy at our institution from 1990 to July 2007 under a waiver of consent granted by the University of Washington Human Studies Committee. The University of Washington Regional Epilepsy Center database contains data back to 1990 and at the time of the query contained information on more than 10,000 patients evaluated at our center. The database of all patients who had already undergone resections was retrospectively queried for terms suggestive of traumatic brain injury, including "trauma," "injury," "contusion," "concussion," "hematoma," or if the term "a positive neurological history" was indicated. A total of 108 patients met the initial screening criteria of possible traumatic brain injury and any surgical cortical resection for treatment of epilepsy. The individual patient records were subsequently reviewed for inclusion and exclusion criteria in which ascertainment of origin and location of resected areas was made (Fig. 1).

Inclusion Criteria

Inclusion criteria for this study were PTE, age ≥ 18 at the time of surgery, long-term video EEG monitoring confirming localization-related epilepsy, preoperative brain CT or MRI, and resection of an extratemporal epilepsy focus, whether it was combined with, preceded, or followed by a temporal lobe resection. The majority of patients who failed to meet the inclusion criteria (77 patients) were excluded because their only surgery was a temporal lobectomy.

Exclusion Criteria

Our exclusion criteria were less than 1 year of follow-up, psychogenic nonepileptic events as the primary diagnosis, or other identified origin for onset of epilepsy (such as birth-related injuries, history of febrile seizures, presence of brain tumors, vascular malformations, or developmental abnormalities of brain cell migration) as determined by either preoperative evaluation or by surgical pathology. We excluded patients for whom the posttraumatic nature of their epilepsy could not be ascertained. For ascertainment we used the following definition for PTE: defined as either a clear history of traumatic brain injury preceding the onset of epilepsy (such as loss of consciousness of hours or greater, hospitalization, skull fracture, and others) or a history suggestive of traumatic brain injury and imaging evidence showing clear evidence of encephalomalacia. If a patient had a vague history of mild head injury and no imaging evidence of encephalomalacia, they were excluded from further analysis. Overall, 4 patients were excluded because they had a vague history of trauma and no lesion on MRI and therefore did not meet our definition of PTE. Five patients were excluded because MRI (or pathology later) showed another origin for their epilepsy (3 with focal cortical dysplasia, 1 with schizencephaly, and 1 with a cavernoma). One patient was excluded because he had less than 1 year of follow-up. A total of 21 patients met both inclusion and exclusion criteria.

Outcome Assessment

Demographic data, imaging abnormalities, interarterial amobarbital angiography (Wada examination) results, and trauma history were extracted from medical records. Patients were assigned a trauma severity score of 1–4 based on history: 1 = minor trauma or no description of the event; 2 = loss of consciousness; 3 = skull fracture, intracranial bleeding without surgery, evidence of encephalomalacia on imaging; and 4 = intracranial bleeding that prompted surgical evacuation, coma, and/or remaining neurological deficit. Outcomes are reported from our database in two forms, the University of Washington classification (Table 1)[17] and the Engel classification[8] (Table 2).

Statistical Analysis

All statistical calculations were performed using Microsoft Excel software. The only statistical test employed was the Fisher exact probability analysis of the results, calculated using Microsoft Computational Biology Webtools: http://research.microsoft.com/en us/um/redmond/projects/MSCompBio/FisherExactTest/. A probability value < 0.05 was considered statistically significant.

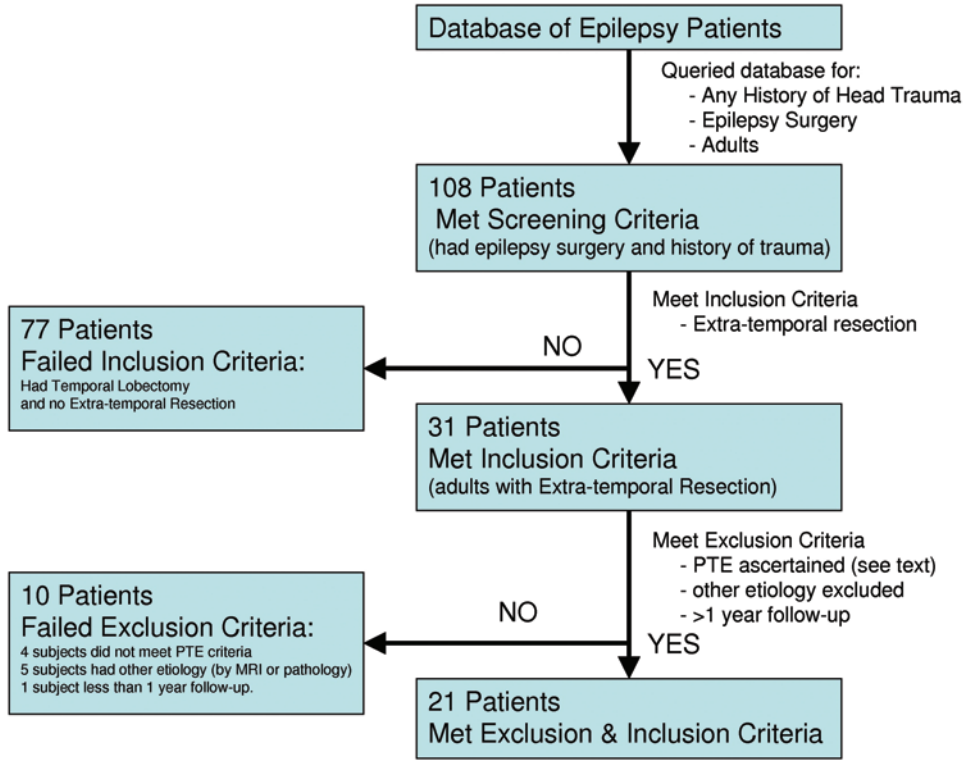

Fig. 1. Flow chart showing inclusion and exclusion criteria for study. Of 108 patients screened from the database for trauma etiology and surgery, 21 met the inclusion criteria. Patients with temporal lobectomy alone or, upon further review, did not have trauma as the primary origin, were excluded.

Results

The results are summarized in Tables 3 and 4, sorted according to surgical outcome at last follow-up in Table 4. Overall, 21 patients, 12 male and 9 female, met our inclusion and exclusion criteria. Most were right-handed (18 patients). The seizure focus was most commonly lateralized to the hemisphere contralateral to the dominant hand (16 cases). The mean age at trauma was 15.7 years (range 1–42 years) and the mean age at epilepsy diagnosis was 19.4 years. Presurgical long-term video EEG evaluation was performed on average 12.9 years after diagnosis (range 0–34 years). The mean age at surgery was 34.7 years (range 19–46 years). Mean follow-up was 7 years.

The cause of trauma was varied, with sports injuries (such as sledding accidents), falls, motor vehicle accidents, and blunt trauma all similarly common. Eight patients had mild or moderate injuries with brief or no loss of awareness at the time of injury, whereas 12 patients had moderate to severe injuries. One patient had multiple injuries, at different times, having experienced both moderate and severe injuries. Additional risk factors and medical conditions are as noted in Table 3 including family history of epilepsy, complications at birth, history of substance abuse, and history of seropositivity for hepatitis B and C, as noted.

Most patients suffered both frequent complex partial and secondarily generalized tonic-clonic seizures, although some reported only partial or generalized convulsions. Patients had been unsuccessfully treated with multiple antiepileptic drugs (average 4.15) and experienced frequent seizures with a wide range of frequencies (Table 3).

Diagnostic evaluation included MRI in most patients, although in 2 patients (Cases 5 and 10, Table 4) only head CT scans were possible. All patients underwent long-term scalp video EEG monitoring. Encephalomalacia was found in the majority (12 patients). Magnetic resonance imaging was normal in 4 patients. The remaining 4 patients had other abnormalities on their MRI, such as focal or global atrophy. Two patients underwent SPECT scans and 1 had a PET scan. Most patients (n = 16) underwent Phase II and Phase III invasive video EEG monitoring with surgically implanted electrocorticography electrodes, most commonly subdural strip and grid electrodes. All had neuropsychological testing and 16 had Wada examinations. Scalp EEG findings (Table 4) included mostly localized interictal and ictal abnormalities.

TABLE 1: Epilepsy surgical outcomes by University of Washington Classification*

Grade	Outcome
a	seizure free except auras
b	nearly seizure free with 2 or fewer seizures per year
c	worthwhile improvement with greater than 75% reduction
d	no worthwhile improvement
e	unknown or unclear

* McKhann et al., 2000.

TABLE 2: Engel classification of epilepsy surgery outcomes*

Classification	Outcome
IA	seizure-free since surgery
IB	nondisabling simple partial seizures since surgery
IC	some disabling seizures after surgery but seizure free for at least 2 years
ID	generalized convulsions with antiepileptic drug discontinuation only
IIA	initially seizure free, has rare seizures now
IIB	rare disabling seizures since surgery
IIC	more than rare disabling seizures since surgery but rare seizures for past 2 years
IID	nocturnal seizures only
IIIA	worthwhile seizures reduction
IIIB	prolonged seizure-free intervals amounting to greater than half the follow-up period and not < 2 years
IV-A	significant seizures improvement
IV-B	no appreciable change
IV-C	seizures worsened

* Engel et al., 1993.

The most common operation was a frontal lobectomy (12 patients). An additional 6 patients had both a frontal lobectomy and a temporal lobectomy. Two of these patients had the frontal and temporal lobectomies during the same surgery, whereas the other 4 had reoperations due to recurrent seizures (most commonly the initial surgery was a temporal lobectomy [in 3 of 4]). The remaining 3 patients had resections in the parietal, posterior temporal-occipital, and temporal-parietal junction, respectively. Two patients had a vagus nerve stimulator implanted after their first 2 operations had failed to control their seizures.

Outcomes are summarized in Table 4 and are based on both University of Washington and Engel classifications. Overall 6 patients (28%) achieved excellent outcomes (seizure free). Six additional patients had rare seizures (2 or fewer per year). Therefore, 12 (57%) of 21 patients had excellent or good outcomes. Five additional patients (24%) had a significant reduction in seizure frequency (University of Washington Class c, corresponding to Engel Class III and IV-A). The remaining 4 patients (19%) did not appear to benefit from surgery.

Patients with encephalomalacia generally did better than other groups (10/12 achieving 2 or fewer seizures per year vs 2/9 without encephalomalacia; $p < 0.01$, Fisher exact test). The outcomes were even better in patients with encephalomalacia who received invasive monitoring, with 5 of 8 seizure free at last follow-up, compared with only 1 of 13 patients without both encephalomalacia and invasive monitoring attaining seizure freedom ($p < 0.014$, Fisher exact test).

Conversely, the patients with normal MRI and poorly localized scalp EEG patterns did less well. Of the patients who had no benefit from surgery, 3 of 4 did not have regions of encephalomalacia and 3 of 4 had poorly localized or bilateral scalp EEG interictal and ictal abnormalities. Four patients had 2 resections during 2 different operations. Only about half of this group had a noticeable reduction in seizure frequency and none was seizure free.

Resections in the speech-dominant hemisphere were less likely to result in good outcomes. When Wada speech lateralization was contralateral to the side of surgery, patients generally did better with all 5 having fewer than 2 seizures per year in this group, compared with 3 of 10 patients who underwent resections on the side of dominant speech. However, no conclusion can be drawn due to the overrepresentation of left hemispheric dominant patients in this small series.

One concern over surgery for PTE is the risk of complications. Surgeries were considered challenging in many of these cases, with longer than usual durations of procedures due to the presence of adhesions and risk for bleeding. Two patients had significant complications. One developed a subdural hematoma and edema after grid placement requiring intracranial pressure monitoring. This patient also had a *Klebsiella* wound infection and a postoperative abscess requiring further surgery. The patient (Case 6, Table 4) nevertheless had a good outcome with seizure freedom achieved 2 years after surgery and no change in neuropsychological performance. Another patient (Case 17, Table 4) had a subdural hematoma in association with invasive monitoring but suffered no significant sequelae from this.

A number of other variables are presented in Tables 3 and 4. However, given the heterogeneity of the population, analysis of other factors such as severity of trauma, relation to age of onset, location of the imaging, and EEG abnormalities was not informative.

Discussion

These results demonstrate that many patients with extratemporal PTE can achieve good to excellent seizure control with epilepsy surgery, with a low risk of complications. The best seizure outcome was noted in patients with a region of encephalomalacia on imaging, in whom invasive video EEG monitoring was performed to optimize the resection. In contrast, only a minority of patients

TABLE 3: Patient characteristics*

		Age (yrs)				Trauma			Seizures		
Case No.	Sex/Handedness	At Trauma	At Diagnosis	LTM	Surgery	Type†	Severity‡	Additional Risk Factors§	Frequency (events/month)	Type¶	No. AEDs Failed
1	M/L	19	22	39	42	sports	4	none	0.4	both	3
2	M/R	34	34	35	37	fall	4	family history (1st degree)	180	both	8
3	M/R	28	35	38	39	blunt	4	none	10	both	3
4	F/R	2	2	36	36	fall	1	family history (1st degree)	150	both	4
5	F/L	3	3	29	29	not described	4	none	30	both	4
6	M/R	17	18	26	26	MVA	4	none	3	both	5
7	F/R	2	10	23	23	fall	1	birth	3	GTC	5
8	M/R	1	22	24	30	multiple	4,2,2	none	1	GTC	5
9	M/R	6	17	18	19	sports	4	none	30	both	3
10	M/R	32	32	42	42	blunt	4	none	0.3	both	4
11	M/L	42	42	42	43	blunt	4	HCV, drugs	4	GTC	2
12	M/R	19	19	43	43	MVA	1	none	3	GTC	2
13	M/R	5	5	19	22	MVA	3	none	5	partial	not reported
14	M/R	9	9	34	34	fall	2	HCV, drugs, family history (remote)	3	GTC	5
15	F/R	14	14	21	22	sports	3	none	2	both	2
16	M/R	17	20	46	46	sports	2	family history (multiple)	2	GTC	4
17	F/R	<10	26	46	46	other	1	HBV, HCV, family history (1st degree)	5	both	5
18	F/R	15	17	17	41	MVA	4	none	360	both	8
19	F/R	12	13	29	29	fall	1	none	12	partial	2
20	F/R	11	13	34	35	sports	2	none	30	both	5
21	F/R	26	35	39	44	fall	3	HCV, drugs, family history (1st degree)	4	both	4

* AED = antiepileptic drug; GTC = generalized tonic-clonic; HBV = hepatitis B infection history prior to surgery; HCV = history of hepatitis C at the time of surgery; LTM = long-term video EEG monitoring; MVA = motor vehicle accident.

† Fall, blunt trauma = being struck or from a fallen object; sports = sports-related trauma such as baseball, sledding, skiing, and others.

‡ Severity scale: 1 = minor trauma or no description; 2 = trauma with loss of consciousness; 3 = trauma with skull fracture, intracranial hemorrhage not requiring evacuation; 4 = severe trauma with intracranial hemorrhage requiring surgical evacuation, coma, and/or remaining neurological deficit.

§ 1st degree = first-degree family members; birth = difficult birth or brief asphyxia at birth; drugs = history of substance abuse; remote = other family members.

¶ In this column, both indicates the presence of both partial and secondarily generalized tonic-clonic seizures; GTC indicates mainly clinical tonic-clonic seizures; and partial indicates mainly simple and complex partial seizures.

TABLE 4: Evaluation and outcome*

Case No.	Scalp EEG Findings		Surgical Data				FU Duration (yrs)	End of FU		First Year		Second Year		Notes
	Interictal†	Ictal	Imaging Results‡	Wada Results§	Invasive EEG	Type of Surgery¶		UWC	Engel Class	UWC	Engel Class	UWC	Engel Class	
1	rt front	rt front	encph	lt/NP	yes	rt front	9.6	a	IA	a	I	a	I	SPECT (lt hemispheric)
2	lt (slow)	lt front	encph	NA	yes	lt pariet & pariet MST	4.7	a	IA	c	III	b	IB or II	
3	rt front	rt front	encph	lt/bilat	yes	rt front	1.8	a	IA	a	I	a	I	
4	lt temp	lt front	bilat temp atrophy	lt/NP	yes	rt front	5	a	IA	a	I	a	I	
5	lt temp	lt temp	encph (CT)	bilat/NP	yes	lt front	6.8	a	IA	NA	NA	NA	NA	
6	bilat front	bilat front	encph	lt/lt	yes	lt front	10.6	a	IA	b	III	a	I	complications (see text)
7	lt & rt temp	lt poorly local but focal appear	lt front atrophy	rt/rt	yes	lt POT	8	b	IB	c	IV-A	c	IV-A	
8	rt front	rt front	encph	lt/lt	yes	rt front	5	b	IB or II	a	I	a	I	
9	lt front & temp	lt front & temp	encph	lt/bilat	yes	lt front	1.4	b	IB or II	b	IB or II	b	IB or II	
10	poorly local but focal appear	rt front	encph (CT)	NA	no	rt front	9	b	IC or II	a	I	a	I	
11	rt central (slow)	rt central	encph	NA	no	rt temp/pariet	12	b	IIB or II	NA	NA	b	IB or II	SPECT (rt temp)
12	lt>rt temp	lt front, rt temp	encph	lt/lt	no	lt temp & lt front	11	b	IID or III	NA	NA	NA	NA	
13	lt front & lt temp	lt>rt temp.	encph	lt/NP	no	lt front, lt temp, VNS	8	c	III or IVA	a	I	c	III	
14	NA	diffuse	rt front, rt temp atrophy	NA	no	rt front	13	c	IIIA	a	I	c	III	
15	lt temp	lt temp	normal	lt/lt	yes	lt temp, lt temp & lt front	1	c	IIIA or IVA	c	IV-A	c	IV-A	PET lt temp hypometabolism
16	lt temp/front	lt front	normal	lt/lt	yes	lt front	1.2	c	IIIA or IVA	c	IV-A	c	IV-A	
17	midline	midline	normal	lt/lt	yes	lt front	8.9	c	IIIA or IVA	c	IV-A	c	IV-A	complications (see text)
18	NA	lt front/temp	encph	NA	yes	lt ATL, lt front, VNS	17	d	IVB	NA	NA	b	IB or II	

(continued)

TABLE 4: Evaluation and outcome* *(continued)*

Case No.	Scalp EEG Findings		Surgical Data				FU Duration (yrs)	End of FU		First Year		Second Year		Notes
	Interictal†	Ictal	Imaging Results‡	Wada Results§	Invasive EEG	Type of Surgery¶		UWC	Engel Class	UWC	Engel Class	UWC	Engel Class	
19	lt>rt temp.	multifocal	lt MTS	lt/NP	yes	lt temp, lt front & lt temp	2.2	d	IVB	d	IV-B	d	NA	
20	gen, lt temp, rt temp	lt front, tonic	rt pariet change	lt/lt	yes	lt front	6	d	IVB	d	IV-B	d	IV-B	
21	rt temp, lt temp, rt front	rt temp poorly local but focal appear	normal	bilat/NP	yes	rt ATL & rt front	6	d	IVC	c	III	c	III	

* ATL = anterior temporal lobectomy; appear = appearing; encph = encephalomalacia; front = frontal; FU = follow-up; gen = generalized; local = localized; MST = multiple subpial transections; MTS = mesial temporal sclerosis; NA = not available; NP = not performed; pariet = parietal; POT = posterior temporal resection; temp = temporal; tonic = appearance of diffuse low-voltage fast EEG changes; UWC = University of Washington Classification; VNS = vagus nerve stimulator.

† Interictal EEG findings were focal epileptiform patterns except for when "slow" is noted, in which case the findings were focal slowing on EEG.

‡ Imaging results are summary of MRI findings. Atrophy = volume loss in a brain region without clear evidence of focal encephalomalacia; change = nonspecific signal changes in a region.

§ Presurgical interarterial amobarbital angiography (Wada) results are presented as language lateralization/memory lateralization.

¶ In patients with more than 1 type of operation during the same craniotomy, results are separated by a comma indicate different procedures at different times, listed in order performed.

with poorly localized foci manifested by normal or nonspecific MRI findings achieved good outcomes.

The results reinforce the value of imaging and parallel those from other publications of PTE surgery.[16] A recent meta-analysis[21] of surgery for intractable epilepsy of diverse origins found median seizure-free rates of 46% with occipital and parietal resections and 27% with frontal lobe resections, with clearly lesional cases achieving much better outcomes. A significant problem for making useful comparisons to other surgical case series is the heterogeneity of the PTE. Etiologies for trauma (such as motor vehicle accidents, falls, and others), age at trauma, definition of PTE (with regard to requirement for presence of MRI abnormality), and local referral patterns have a potential impact on outcomes. When MRI abnormalities are present, the extent of abnormalities can be small and restricted in some cases, but diffuse and multilobar and even bilateral in other cases. Further, since the number of cases is generally small for each surgical center, the specific numbers for PTE are often reported as a small fraction of other case series. Kazemi et al.[14] reported on resection of frontal encephalomalacia for intractable epilepsy, with 8 of the 17 cases having PTE. Almost 60% of the total cohort was seizure free and 10% had rare seizures, with comparable outcomes between the traumatic and nontraumatic cases. Hartzfeld et al.[10] reported the outcomes for 45 patients with PTE including 18 who had seizures originating from nonmesial temporal regions. Among those 18 patients, 6 were seizure free, 5 had rare seizures, and the remaining 7 had less successful outcomes. Many were believed to have neocortical temporal lobe epilepsy. Marks et al.[16] reported outcomes of 25 patients with PTE. Three of the cases had neocortical foci with a well-circumscribed lesion. This group did well. Sixteen patients did not have clear focal MRI findings and were either not offered surgery or did not achieve significant benefit from resection. A recent review of other surgical PTE cases with normal MRI findings indicated that approximately half are extratemporal.[4] Outcomes were not differentiated by origin but are similar to what is reported in this study. Similar results have also been reported for occipital foci[3] without clear differentiation between PTE and other etiologies.

Complication rates in the current series, while higher than in general epilepsy surgery cases, were acceptable, with no permanent deficits. The only complications reported here were in association with invasive monitoring. Due to the presence of adhesions and scar tissue, placement of subdural electrodes involves a higher risk of parenchymal damage and hemorrhage. This poses a significant problem because effective invasive monitoring, as reported here, is associated with better outcomes. Even when used, placement of invasive subdural electrodes in the desired locations is frequently difficult due to the same factors.

Patients with normal MRI and nonpenetrating brain injuries did less well, as is often the case for MRI negative cases.[4,9] Epidemiological studies suggested that patients with mild head trauma are much more likely to develop epilepsy if they have first degree relatives with epilepsy,[5] while the contribution of family history in severe trau-

matic brain injury is more modest. This could mean that the epilepsy in this patient group might not actually be due to trauma, or that a genetic predisposition may be required for the development of epilepsy after milder injuries. Several of the cases excluded from the analysis here were initially considered to be PTE, but later pathology identified another process such as focal cortical dysplasia instead of gliosis. This may give credence to the possibility of trauma being an additional burden in the vulnerable cortex that already has a predisposition to epileptogenesis.

There are many limitations to the current study. Most significantly, the presented data are from a single center and involves only 21 patients. Furthermore, the data presented spans many years and the technology has evolved over that time period. Another weakness of this study is the limited use of additional neuroimaging tools such as SPECT and PET in assessing these candidates. Particularly in the normal MRI group, finding anatomical evidence of the seizure focus is particularly useful. This was not performed in many of the cases here. Our current practice has changed, utilizing these tests more as the technology becomes more available and practical. Use of PET may have a limited role when lesions are noted on MRI, because PET findings may simply match the MRI abnormalities. Use of SPECT also has many logistical challenges in delivering the isotope to the right seizure and at the right time. Nevertheless, these studies could be helpful in guiding electrodes for invasive monitoring.

The retrospective nature of this study limits the implications of the results for surgical decisions. For example, it cannot be determined how many patients were evaluated and found not to be good surgical candidates. Similarly, because of perceptions about risk of surgery or poor success, some patients may have been discouraged from pursuing evaluation for epilepsy surgery.

Because we excluded cases of temporal lobectomy alone, this study does not address the full spectrum of PTE. In addition to the role of multiple brain regions involved in trauma, the multifocal nature of the cases we describe could speak to the nature of posttraumatic epileptogenesis as suggested by recent animal models. Even a focal traumatic injury can lead to a wide variety of chronic seizure conditions.[6,7]

Some of our results have unclear significance. For example, the disproportionate number of speech-dominant hemisphere cases means that caution must be taken interpreting the finding of worse seizure outcomes in the speech-dominant hemisphere. However, this could be due to the fact that a larger resection may be possible with nondominant hemisphere resections. Although frontal lobe resections were most common in our series, we cannot draw reliable conclusions as to the relative risk of intractability with different brain regions, because we have not identified those patients with PTE who did not undergo surgical treatment.

Until epileptogenesis can be effectively prevented, traumatic brain injury will remain a significant risk factor for medically intractable epilepsy. This study demonstrates that many patients with this common condition can be safely and effectively treated with neurosurgery, even in the more challenging cases of extratemporal foci.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Kershenovich, Miller, JG Ojemann. Acquisition of data: Kershenovich, Hakimian. Analysis and interpretation of data: Kershenovich, Hakimian, Miller, JG Ojemann. Drafting the article: Kershenovich, Hakimian. Critically revising the article: Kershenovich, Hakimian, Miller, JG Ojemann, D'Ambrosio. Reviewed submitted version of manuscript: all authors. Statistical analysis: Kershenovich, Hakimian. Administrative/technical/material support: Hakimian. Study supervision: Miller, JG Ojemann, Hebb, GA Ojemann.

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Vagus nerve stimulation after lead revision

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Object. Vagus nerve stimulation (VNS) has demonstrated benefit in patients with medically intractable partial epilepsy. As in other therapies with mechanical devices, hardware failure occurs, most notably within the VNS lead, requiring replacement. However, the spiral-designed lead electrodes wrapped around the vagus nerve are often encased in dense scar tissue hampering dissection and removal. The objective in this study was to characterize VNS lead failure and lead revision surgery and to examine VNS efficacy after placement of a new electrode on the previously used segment of vagus nerve.

Methods. The authors reviewed all VNS lead revisions performed between October 2001 and August 2011 at the University of Iowa Hospitals and Clinics. Twenty-four patients underwent 25 lead revisions. In all cases, the helical electrodes were removed, and a new lead was placed on the previously used segment of vagus nerve. All inpatient and outpatient records of the 25 lead revisions were retrospectively reviewed.

Results. Four cases were second lead revisions, and 21 cases were first lead revisions. The average time to any revision was 5 years (range 1.8–11.1 years), with essentially no difference between a first and second lead revision. The most common reason for a revision was intrinsic lead failure resulting in high impedance (64%), and the most common symptom was increased seizure frequency (72%). The average duration of surgery for the initial implantation in the 15 patients whose VNS system was initially implanted at the authors' institution was much shorter (94 minutes) than the average duration of lead revision surgery (173 minutes). However, there was a significant trend toward shorter surgical times as more revision surgeries were performed. Sixteen of the 25 cases of lead revision were followed up for more than 3 months. In 15 of these 16 cases, the revision was as effective as the previous VNS lead. In most of these cases, both the severity and frequency of seizures were decreased to levels similar to those following the previous implantation procedure. Only 1 complication occurred, and there were no postoperative infections.

Conclusions. Lead revision surgery involving the placement of a new electrode at the previously used segment of vagus nerve is effective at decreasing the seizure burden to an extent similar to that obtained following the initial VNS implantation. Even with multiple lead revisions, patients can obtain VNS efficacy similar to that following the initial lead implantation. There is a learning curve with revision surgery, and overall the duration of surgery is longer than for the initial implantation. Note, however, that complications and infection are rare.
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Key Words • epilepsy • seizure • vagus nerve stimulation • neuromodulation • vagus nerve

Vagus nerve stimulation is a useful adjunct to the armamentarium of surgical options for the treatment of epilepsy.[10,11,14] Studies in the 1990s demonstrated a mean 25%–30% decrease in seizure frequency in epilepsy patients following VNS, which led to US FDA approval in 1997 for the treatment of intractable partial epilepsy in patients older than 12 years of age.[4,9,21] To date, many more retrospective and nonrandomized studies have confirmed the effectiveness of VNS in children[7] and adults afflicted with treatment-resistant epilepsy.[5,6] Further therapeutic uses for VNS are currently being investigated and include early but encouraging results for depression[13] and heart failure.[18] Although peripheral nerve stimulation to treat seizures is not a new concept, the exact mechanism through which VNS decreases the seizure burden is not completely understood.[22]

As with most mechanical devices, hardware failure can occur in VNS for various reasons.[20] Failure or depletion of the IPG or failure of the VNS lead can result in improper device function and ineffective seizure control.[20] Replacing the IPG typically yields expected device function, even with multiple IPG replacements, and complications are uncommon. Lead revision can be more challenging, however (Fig. 1). The spiral-designed lead electrodes wrapped around the vagus nerve are often encased in dense scar tissue hindering dissection and removal (Fig.

Abbreviations used in this paper: IPG = implantable pulse generator; UIHC = University of Iowa Hospitals and Clinics; VNS = vagus nerve stimulation.

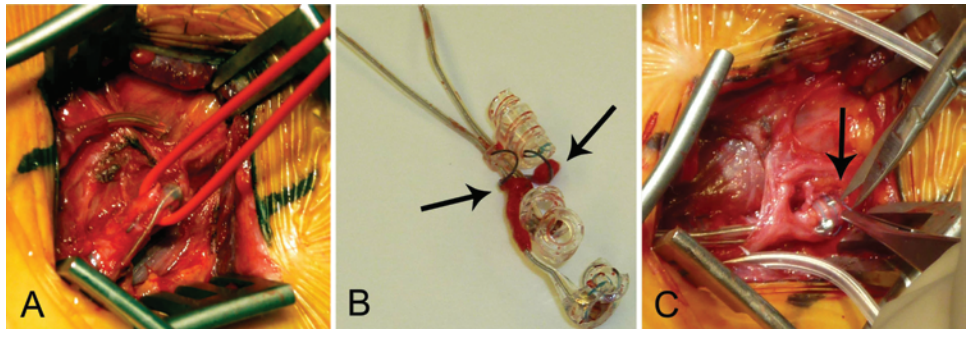

Fig. 1. Photographs obtained during VNS lead revision surgery. **A:** A vessel loop around the vagus nerve and a VNS lead encased in dense fibrous scar tissue. **B:** *Arrows* indicate scar tissue attached to lead cable strings. **C:** Placement of new VNS lead on same segment of vagus nerve and removal of helical electrode strings with scissors *(arrow)*.

1A and B).[16] The etiology of lead failure, time to failure, and complication rate of lead revision have not been fully elucidated. Furthermore, VNS efficacy is unclear after placement of a new electrode on the previously used segment of vagus nerve encased in scar tissue (Fig. 1C). There are relatively few studies that characterize VNS lead revision and discuss VNS efficacy in seizure reduction following a revision as compared with effectiveness following the initial lead implantation.

Methods

Patient Population

After the University of Iowa Institutional Review Board approved the study, all VNS lead implantations were identified through a neuromodulation patient registry. Two hundred twenty-three VNS lead implantations were performed between October 2001 and August 2011 at the UIHC. One hundred ninety-eight patients underwent initial VNS implantations, and 24 underwent 25 VNS lead revisions. Among these 25 revision cases, the previous VNS lead had been implanted at UIHC in 15 cases and at another institution in 10.

All patients were treated by a single neurosurgeon (H.K.). All inpatient and outpatient records were retrospectively reviewed, and the following data were recorded: patient age, sex, age at lead implantation or revision, date of last follow-up, seizure modality, frequency of seizures before and after initial lead implantation and before and after lead revision, lead failure symptoms, lead impedance at revision, lead fracture, history of VNS system–related infection, recent head or neck trauma, surgical findings, use of microscope, and postrevision complications and infection.

Prior to VNS implantation, all patients underwent evaluation at a multidisciplinary epilepsy surgery conference and were recommended for surgery. A multidisciplinary approach was also conducted for VNS lead revision, and the decision to perform a revision was based on lead impedance, integrity of the lead and IPG, patient symptoms, and seizure frequency. Vagus nerve stimulation therapy in patients with generalized epilepsy and in children younger than the age of 12 years is an off-label use and is not approved by the FDA.

Surgical Technique: Initial Implants

Initial implantations in all patients were performed using standard VNS techniques. In brief, all VNS leads (Cyberonics, Inc.) were placed on the left vagus nerve while patients were under general anesthesia. A left-sided transverse neck incision from the sternocleidomastoid to the midline was made for neck dissection and vagus nerve exposure for lead implantation. An infraclavicular chest incision was performed for IPG placement, and leads were tunneled subcutaneously from the neck to the chest incision. In each patient the lead and IPG were implanted in a single operation. Prophylactic perioperative antibiotics—nafcillin or vancomycin if the patient was allergic to penicillin—were used for all implantation surgeries, beginning at least 30 minutes prior to incision and continuing for 24 hours postoperatively.

Surgical Technique: Revisions

In brief, revision surgery was performed through the previous surgical incision on the left without increasing the length of the incision. A sharp left-sided neck dissection was performed to access the VNS helical lead electrodes (Fig. 1A). The old VNS lead was removed (Fig. 1B), and a new lead was placed on the segment of vagus nerve used by the previous electrode (Fig. 1C). In nearly all cases, the IPG was replaced at the infraclavicular pocket at the time of lead revision. In the first 9 lead revisions, the microscope was used for dissection of the old lead from the vagus nerve. Magnification with loupes was used in the last 16 revisions. All other aspects of lead revision were similar to the initial implantation.

Results

Patient Demographics and Characteristics

Twenty-four patients underwent 25 VNS revisions between October 2001 and August 2011 at UIHC (Table 1). Of these 25 revisions, 4 were second and 21 were first lead revisions. There were 15 male (62.5%) and 9 female (37.5%) patients, of whom 23 were adults (96%). The most common type of epilepsy was partial, with 22 (92%) of 24 patients having some form of partial epilepsy. The mean patient age at the previous implantation was 32 years

TABLE 1: Summary of data in 25 cases of VNS lead revision*

Case No.	Sex	Revision No.	Time to Revision (yrs)	Impedance	Lead Fracture	History of VNS Infection	Lead Failure Symptoms	Sz Frequency After Revision†
1	M	1st	3.8	high	no	no	increased Szs	decreased
2	M	2nd	3.7	high	yes	no	increased Szs	unknown
3	M	1st	7.4	high	no	no	increased Szs	decreased
4	F	1st	1.8	high	no	no	none	decreased
5	F	2nd	3.3	high	no	no	none	decreased
6	F	1st	3.4	high	no	no	increased Szs	unknown
7	F	1st	11.1	high	no	no	increased Szs	decreased
8	M	1st	3.4	high	no	no	increased Szs & shock sensation	unknown
9	M	1st	6.8	high	no	no	increased Szs	increased
10	F	1st	1.8	high	no	no	increased Szs	decreased
11	F	1st	7.0	high	no	no	increased Szs	unknown
12	M	1st	6.0	NA	no	yes	NA	unknown
13	F	1st	6.3	normal	yes	no	increased Szs	decreased
14	M	1st	4.2	high	dislocated	no	none	unknown
15	M	1st	2.6	high	no	no	none	decreased
16	M	1st	8.4	short circuit	no	no	increased Szs	unknown
17‡	M	1st	5.4	high	no	no	increased Szs	decreased
18	F	1st	5.3	high	no	no	increased Szs	decreased
19	M	1st	2.3	normal	no	no	increased Szs & shock sensation	decreased
20	M	1st	3.4	high	no	no	increased Szs	decreased
21	M	1st	6.3	high	no	no	increased Szs	decreased
22	F	2nd	4.2	normal	no	yes	increased Szs & neck/chest pain	unknown
23	F	1st	5.6	short circuit	no	no	increased Szs & paresthesias	decreased
24	M	2nd	8.0	high	no	yes	none	unknown
25	M	1st	4.3	normal	yes	no	none	decreased

* NA = not applicable; Sz = seizure.

† As compared with prior to surgery and before initial VNS implantation.

‡ Patient with postoperative cable bowstring complication requiring revision 1 month later.

(range 4–55 years), and the mean age at lead revision was 37 years (range 8–59 years). The mean age of patients with first lead revisions was 35 years (range 8–59 years), and those with second lead revisions, 46 years (range 26–59 years). The average time to any lead revision was 5 years (range 1.8–11.1 years), with essentially no difference between a first and second lead revision. The average time to a first lead revision was 5.1 years and that to a second lead revision was 4.8 years. Time to lead revision for each type of lead failure is presented in Table 2.

Lead Impedance

Interrogation of the VNS system and determining lead impedance allow one to assess the integrity and function of the system. The deviation of impedance from normal may indicate improper device function. The patients in 18 cases (72%) presented with high impedance at the time of revision, 2 cases (8%) involved a short circuit within the system, 4 cases (16%) demonstrated normal impedance, and 1 case (4%) had no implanted VNS system and therefore no impedance reading since the system had been previously removed at another institution because of infection.

Lead Failure Etiology

The determination of lead failure (Table 2) relies on a patient's clinical symptoms, seizure frequency, and interrogation of the system and lead impedance. Sixteen (64%) of the 18 cases with high impedance at the time of revision had no visible damage or fracture within the lead and/or cable, suggesting an intrinsic lesion within the lead and/or cable. Other causes of lead failure included visible fractures of the lead in 3 cases (12%), increasing seizure frequency and an impedance indicating a short circuit in 2 cases (8%), normal impedance but pain and shock-like sensations suspect for device malfunction in 2 cases (8%), electrode coil dislocation from the vagus nerve in 1 case (4%), and a previous hardware infection and VNS system removal in 1 case (4%).

Lead Failure Symptoms

Symptoms vary depending on the etiology of lead

TABLE 2: Summary of lead failures in 25 cases of lead revision

Type of Failure	No. (%)	Mean Time to Lead Revision (yrs)
intrinsic (microlesion)	16 (64)	5.1
visible fracture	3 (12)	4.8
short circuit	2 (8)	7
other device malfunction	2 (8)	3.3
electrode coil dislocation	1 (4)	4.2
infection	1 (4)	6

failure (Table 1). The patients in 18 cases (72%) presented with increased seizure frequency; in 4 cases (16%), with neck and/or chest pain, paresthesias, or shock-like sensations—all probably the result of a short circuit within the system; and in 6 cases (24%), with no new symptoms. Additionally, 3 cases (12%) had a history of VNS-related infection, and 3 cases (12%) had a recent history of head and/or neck trauma.

Lead Revision Surgery

The average duration of surgery for the initial implantation in 15 patients whose VNS system was implanted at our institution was 94 minutes (range 53–195 minutes) and occurred between January 2002 and March 2008 (Fig. 2). The average duration of lead revision surgery was 173 minutes (range 108–273 minutes) and occurred between October 2005 and July 2011. The duration of the revision surgery decreased as the experience of the surgeon increased over time. In all cases, the vagus nerve was found encased in fibrous scar tissue (Fig. 1A and B). In the first 9 revision cases (between October 2005 and March 2009), a surgical microscope was used to dissect the VNS lead free from the nerve. In the last 16 revision cases (between April 2009 and July 2011), only loupe magnification and headlight illumination were used. In all cases, sharp dissection was performed. There were no postoperative infections. Only 1 patient experienced a complication requiring additional surgery; in this patient the lead cable was taut, creating a pulling sensation on neck turning.

Seizures Before and After VNS System Implantation and Lead Revision

Sixteen of the 25 cases of VNS lead revision were followed up for longer than 3 months at our institution to fully assess the efficacy of seizure treatment. In 15 (94%) of these 16 cases, the revision was as effective as the previous VNS system. In almost all cases, both the severity and frequency of seizures were decreased to levels similar to those following implantation of the initial VNS lead. Of the 4 second lead revisions, only 1 was followed up for longer than 3 months; this patient was found to have seizure control similar to that obtained after both the previous and the initial VNS implantation. The average follow-up in these patients was 21 months (range 3–55 months).

Discussion

Vagus nerve stimulation is an effective and generally safe treatment option for patients with medically intractable epilepsy.[3] Randomized controlled studies in the 1990s demonstrated a 25%–30% decrease in seizure frequency, which led to FDA approval of VNS for partial epilepsy.[4,9,21] Since its approval, VNS implantations have been widely performed.[6] Given the increasing use of VNS for the treatment of medically intractable epilepsy, however, VNS lead failure is more commonly observed.[1,8,12,15–17,19,20] The determination of lead failure relies on multiple factors, including the patient's clinical symptoms, seizure frequency, and interrogation of the system and lead impedance. We found that lead failure occurs for a variety of reasons and in our series was most commonly observed in cases of high impedance within the VNS lead, which was found in 72% of our lead revisions (Table 1). The majority of patients (89%) who presented with high impedance had no visible damage or gross fracture of the lead or cable. The etiology of high impedance and lead failure is not entirely clear in these cases. Some have ascribed lead failure in the absence of a visible fracture

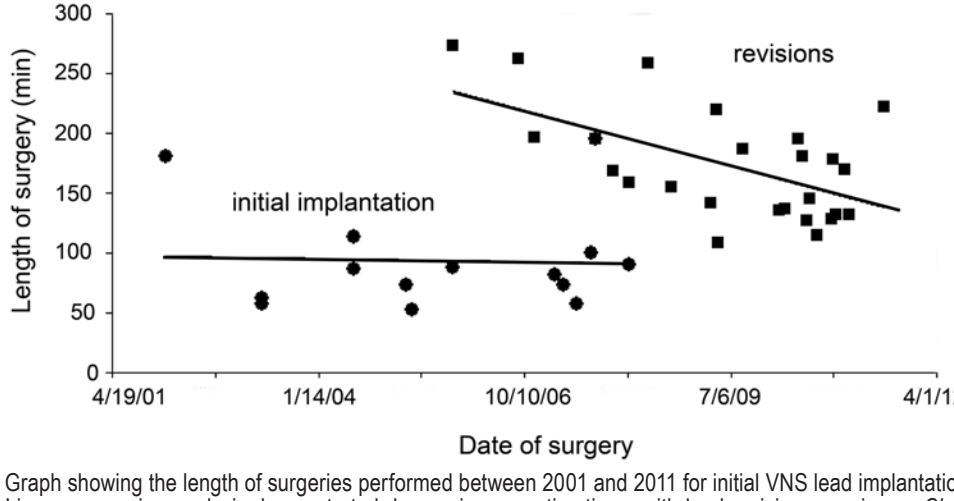

Fig. 2. Graph showing the length of surgeries performed between 2001 and 2011 for initial VNS lead implantations and lead revisions. Linear regression analysis demonstrated decreasing operative times with lead revision experience. *Circles* indicate initial implantations; *squares*, revisions.

to "microlesions" within the lead cable,[20] whereas others have observed lead failure without visible fractures in which they believed that significant vagus nerve scar tissue resulted in high impedance.[15] However, we found that the placement of a new VNS lead at the previously used segment of vagus nerve provided a proper contact in all 16 such cases as well as normal impedance, implying that the presence of dense scar tissue was probably not the cause of lead failure.

In addition to an intrinsic increase in lead impedance and device failure, we observed other factors resulting in lead failure. We have found and others have observed, albeit a rare event, visible fractures within the lead cable resulting in physical disconnection and lead failure.[20] Additionally, dislocated leads,[20] hardware-related infection,[2] device malfunction, and short circuits within the system were noted.[20] Imaging of the neck and chest with radiography can often be used to diagnose visible fractures[17] and dislocated lead coils.[20] It is unclear at this time if there are any risk factors that may predispose someone to a specific type of lead failure. An attempt was made to correlate any recent head or neck trauma with lead failure, but in our series trauma was an uncommon occurrence.

In our study, VNS lead failure most commonly resulted in an increased seizure frequency. In some cases, a very dramatic increase in seizure intensity and frequency was observed. However, other symptoms alerted patients to device malfunction and included neck and chest pain, shock-like sensations, and paresthesias. Short circuits within the system may cause these types of symptoms. The stimulator should be turned off immediately if this occurs and interrogated. As in our series, other studies have shown that these shock-like sensations,[12] pain, and paresthesias will resolve after revision.[20]

We used time from previous lead implantation to lead revision to approximate the time to lead failure (Table 2). Determining the exact point of malfunction or failure isn't always possible because VNS may have some efficacy even after device malfunction. Overall, it appears that the variation in the length of time to VNS lead failure is notable and that the average time to failure (5 years) is comparable to that in other smaller studies.[8] This average time to failure was mostly influenced by and most representative of intrinsic lead failures, as they constituted the majority of our cases.

Vagus nerve stimulation lead revision can be challenging. As surgeon experience with lead revisions increases, the operative time decreases significantly. In our study, however, given the presence of scar tissue, it remains a longer operation than the initial implantation. Initially, the use of an intraoperative microscope probably contributed to longer surgical times. Although the normal anatomy was obscured and altered by scar tissue in all cases, we had only 1 complication after lead revision. Other authors have noted complications after lead revision including transient vocal cord paralysis.[17] There were no infections postoperatively and therefore no increase in the postoperative infection rate as compared with historical averages.

To more efficiently, safely, and effectively revise the VNS lead, others have provided a discussion of surgical techniques. Some have advocated the use of sharp dissection,[12] whereas others have endorsed sharp monopolar cautery[15] to aid dissection in which dense fibrous tissue is encountered. Still others have attempted to access a naive segment of the nerve.[12] Given the dense scar tissue, some surgeons cut the distal lead and leave the helical leads in place while a naive segment of the vagus nerve is dissected for placement of the new lead. To avoid the fibrous scar tissue, O'Neill and Wilberger[16] described a posterior cervical triangle approach to a naive segment of the vagus nerve. In both the initial implantation and the lead revision, we used sharp dissection through the previous surgical incisions. Additionally, in an attempt to decrease scar tissue formation around the vagus nerve, we routinely cut the strings off of the helical loops of the VNS lead on implantation (Fig. 1C). We cannot yet comment on whether this strategy is effective in decreasing scar tissue formation.

We observed that VNS lead revision is effective at decreasing the seizure burden to an extent similar to the previous implantation, in agreement with previous reports.[1,12] More specifically, using the previously utilized segment of vagus nerve for lead revision is as effective as the previous implantation. Among the larger series in the literature, the study in a pediatric population by Agarwal et al.[1] documented treatment efficacy, that is, decreased seizure frequency and severity, similar to that in our series. These authors retrospectively examined the records of 23 patients who underwent VNS lead revision through a combination of techniques and found that the efficacy of the new implant did not appear to be altered by revision surgery. It is unclear in how many cases these authors placed the new electrode on the previously used segment of vagus nerve or on a naive segment. Other smaller studies have also demonstrated a return to previous seizure control with lead revision.[12]

Study Limitations

We demonstrate in a large series of patients the effectiveness of VNS lead revision at the previous site of implantation. However, there are study limitations. As with all retrospective studies, there is inherent bias in our study. A prospective study would better estimate the etiology of lead failure and time to lead failure. Additionally, the widespread use of VNS is recent. The average time to failure and the type of failure may change over time. When analyzing therapeutic success, a regression to the mean should be considered. Seizure frequency fluctuates for many reasons in patients with epilepsy, and this may account for some seizure reduction following lead revision. However, in many of our cases, not only was seizure frequency increased, but interrogation of the VNS system also revealed abnormal impedance, indicating lead failure as well. Other confounding variables include the changing antiepilepsy drugs patients potentially received over the follow-up period. Furthermore, as others have mentioned, the clinical absence of dysphonia or aspiration does not preclude the possibility of vagus nerve injury, and therefore underreporting of actual injury may be present. Further prospective studies of VNS lead revisions will help to elucidate many of these limitations.

Conclusions

Vagus nerve stimulation lead revision surgery with placement of a new electrode at the previously used segment of vagus nerve is effective in decreasing the seizure burden to an extent similar to the initial VNS implant. Even with multiple lead revisions, patients can obtain seizure control similar to that following the initial lead implantation. There is a learning curve with revision surgery, and overall the duration of a revision surgery is longer than the initial implantation. However, complications and infection are rare.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Vagal nerve stimulation for the treatment of medically refractory epilepsy: a review of the current literature

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Object. The authors conducted a study to evaluate the published results of vagal nerve stimulation (VNS) for medically refractory seizures according to evidence-based criteria.

Methods. The authors performed a review of available literature published between 1980 and 2010. Inclusion criteria for articles included more than 10 patients evaluated, average follow-up of 1 or more years, inclusion of medically refractory epilepsy, and consistent preoperative surgical evaluation. Articles were divided into 4 classes of evidence according to criteria established by the American Academy of Neurology.

Results. A total of 70 publications were reviewed, of which 20 were selected for review based on inclusion and exclusion criteria. There were 2 articles that provided Class I evidence, 7 that met criteria for Class II evidence, and 11 that provided Class III evidence.

The majority of evidence supports VNS usage in partial epilepsy with a seizure reduction of 50% or more in the majority of cases and freedom from seizure in 6%–27% of patients who responded to stimulation. High stimulation with a gradual increase in VNS stimulation over the first 6 weeks to 3 months postoperatively is well supported by Class I and II data. Predictors of positive response included absence of bilateral interictal epileptiform activity and cortical malformations.

Conclusions. Vagal nerve stimulation is a safe and effective alternative for adult and pediatric populations with epilepsy refractory to medical and other surgical management.
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Key Words • vagal nerve stimulator • intractable epilepsy • surgical treatment of epilepsy • medically refractory epilepsy

Seventy percent of patients with epilepsy can be treated successfully with 2 or fewer antiepileptic medications, leaving 30% of patients who suffer the additional risk of breakthrough seizures or intolerable side effects of additional medication.[7,29] Prior to the availability of VNS, surgical options for refractory epilepsy focused mainly on resective strategies, including anatomical and/or functional temporal lobectomies or lesionectomies.[13] These procedures have been proven viable for patients with lesions identifiable on imaging or electrophysiological studies supporting a focal ictus and render 60%–90% seizure free. However, for those patients in whom these criteria are not met, resection has shown equivocal results.[6,7]

Intermittent stimulation of the left cervical vagus nerve has been shown to reduce the frequency and intensity of seizures, but it has failed to show any visible electroencephalographic changes.[16] Putative targets of VNS activity have included multiple thalamic and brainstem sites proposed to desynchronize thalamocortical circuitry involved in seizure propagation.[12,16,18,20,21] Zabara[30] has demonstrated afferent projections from the vagus nerve, traveling within the nucleus tractus solitarius synapsing in the locus coeruleus and raphe magnus nuclei with effects on the release of norepinephrine and serotonin.

While the mechanism of action of VNS in diminishing the frequency and intensity of seizure activity remains undetermined, multiple clinical investigations have supported its continued use in both the adult and pediatric populations. According to the most recent position statement from the American Academy of Neurology, VNS is indicated for "adults and adolescents over 12 years of age with medically intractable partial seizures who are not candidates for potentially curative surgical resections, such as lesionectomies or mesial temporal lobectomies."[12]

We propose, utilizing evidence-based classification and guidelines, to perform a review of the currently available literature on the application of VNS in patients with medically refractory epilepsy.

Abbreviations used in this paper: RCT = randomized controlled trial; VNS = vagal nerve stimulation.

Methods

An English-language literature search on the use of VNS for the treatment of medically refractory epilepsy was performed utilizing Medline/PubMed search strings including "vagal nerve stimulation," "epilepsy," "outcome," and "efficacy." This search was further limited to articles regarding humans that were published between 1980 and 2011. To complete the final list of publications for review, a search of relevant references from each of the resulting articles was performed. This group was then examined for inclusion or exclusion in the final analysis based on the following criteria: more than 10 patients evaluated, average follow-up of 1 or more years, inclusion of medically refractory epilepsy, and consistent preoperative surgical evaluation (Table 1).

Each article was classified as providing Class I, Class II, Class III, or Class IV evidence according to the criteria of the American Academy of Neurology. Class I evidence was characterized as a prospective clinical RCT with masked outcome assessment in a representative population; Class II evidence was defined as a prospective matched-group cohort study in a representative population with masked outcome assessment; Class III evidence was defined as all other controlled trials in which outcome assessment was independent of patient treatment; and Class IV evidence was defined as all uncontrolled trials including case reports.

Results

A Medline search and review of reference lists yielded 70 articles meeting search-string criteria. After applying inclusion and exclusion criteria, 20 articles were included in the final investigation: 15 studies focused primarily on an adult population and 5 focused exclusively on a pediatric population. Two studies[5,17] met criteria for Class I evidence, 7 as Class II evidence, and 11 as Class III evidence. The mean number of cases investigated per study was 90.7 (range 16–436 cases) with a median of 62 patients. The mean minimum postoperative follow-up was 10.5 months (range 3–24 months).

The majority of publications reported outcome in terms of the frequency of seizure reduction with the majority segregating cases into those with a 50% or greater reduction versus those with less than a 50% reduction. There were 14 publications that used this standard, and of the 1378 patients studied, a mean of 50.9% (range 18.4%–67%) showed a 50% or greater decrease in seizure frequency.[1,2,4,5,8–11,15,24–28] Five of the remaining studies used the mean or median frequency reduction from baseline.[3,14,17,22,23] The mean seizure reduction in these investigations was 42.8% (range 28%–66%). Four studies additionally included data on the percentage of patients achieving freedom from seizures, typically quoted at the 1-year time frame.[9,15,19,28] Of these studies, seizure freedom was reported at a mean of 14.0% (range 9%–27%).

TABLE 1: Summary of class of data, number of patients studied, minimum follow-up, and percentage of patients achieving seizure freedom and 50% or greater reduction in seizure frequency in publications investigating outcome in VNS*

Authors & Year	Evidence Class	No. of Patients	Min FU (mos)	% of Patients	
				Seizure-Free Status	≥50% Reduction
Ben-Menachem et al., 1994	I	67	3.5	—	38.7
Handforth et al., 1998	I	196†	3.0	—	—
George et al., 1994	II	67	16.0	—	—
Ben-Menachem et al., 1995	II	16	9.0	—	—
Salinsky et al., 1996	II	100	24.0	—	18.4
Ben-Menachem et al., 1999	II	64	3.0	—	40.4
Vonck et al., 1999	II	15	12.0	27.0	67.0
Sirven et al., 2000	II	45	3.0	—	67.0
Ardesch et al., 2007	II	19	12.0	—	36.8
Janszky et al., 2005	III	47	12.0	13.0	—
Murphy, 1999	III	60	3.0	—	—
Chavel et al., 2003	III	29	24.0	—	61.0
Murphy et al., 2003	III	96	6.0	—	45.0
Benifla et al., 2006	III	41	6.0	—	3.8
Saneto et al., 2006	III	43	9.0	—	51.0
De Herdt et al., 2007	III	138	12.0	9.0	59.0
Montavont et al., 2007	III	50	21.6	—	—
Ghaemi et al., 2010	III	144	24.0	6.9	61.8
Elliott et al., 2011[10]	III	436	3.0	—	63.7
Elliott et al., 2011[11]	III	141	3.0	—	64.8

* FU = follow-up; — = not reported.

† Value reflects the intent-to-treat population.

Class I Evidence

There were 2 RCTs investigating the efficacy of VNS in reducing seizure activity in medically refractory epilepsy. In 1994, Ben-Menachem et al.[5] evaluated 67 patients with intractable seizures in a multicenter, randomized, parallel, double-blind study identified as E03. After a 12-week baseline recording of seizure frequency, patients were randomized to either a high- or low-stimulation 14-week VNS treatment. Plasma antiepileptic drug concentrations were maintained throughout the study. Thirty-one patients receiving high-stimulation VNS experienced a mean seizure frequency percentage reduction of 30.9%, whereas 36 patients receiving low-stimulation VNS had mean seizure reduction of 11.3%. These values were found to be statistically significant

In 1998, Handforth et al.[17] evaluated 254 patients, 13–60 years of age, with intractable partial seizures in a multicenter, double-blind, randomized, active-control study identified as E05. The patients were required to have at least 6 complex partial, visible partial motor, or secondarily generalized seizures in the month prior to entry. After a 12- to 16-week baseline recording, patients were randomly assigned to a high- or low-stimulation group. The 94 patients receiving high stimulation had a mean reduction in seizure frequency of 28%, whereas the 102 patients receiving low stimulation had a 15% reduction. No significant difference was found between the 2 groups in terms of individuals experiencing a 50% or greater reduction in seizure frequency; however, those experiencing a 75% or greater reduction were statistically more likely to be in the high-stimulation group.

Class II Evidence

The 7 studies meeting criteria for Class II evidence were all prospective cohort investigations designed to assess outcome in long-term follow-up of VNS patients. George and colleagues[14] prospectively followed 67 of the patients initially randomized in the E03 study for an additional 16–18 months. The population included 31 patients initially receiving high stimulation and 36 receiving low stimulation. During this investigation, all patients now received high stimulation. Both groups showed a significant decrease in seizure frequency compared with baseline. The patients initially randomized to the high-stimulation group had a 52.0% mean seizure frequency reduction, whereas those in the low-stimulation group had a reduction of 38.1% compared with baseline. Salinsky and associates[25] performed a similar open-label extension of an RCT in which 100 patients showed significant reductions in seizure frequency with 1 year of prospective follow-up.

Ardesch et al.[1] prospectively evaluated 19 patients with medically refractory epilepsy for a period of 2–6 years (mean 4 years). Their results show a gradual but significant reduction in seizures over the 6 years of study with an approximately 50% reduction in seizure frequency after 5 years. They additionally found a positive effect on seizure severity, seizure duration, and postictal period.

Ben-Menachem and coworkers[4] also found positive results in the long-term follow-up of 64 patients with various refractory epileptic disorders. They reported a 50% or greater seizure reduction in patients with partial seizures, idiopathic generalized seizures, and Lennox-Gastaut syndrome with treatment up to 5 years. Overall, 44% of the patients showed response to treatment.

Class III Evidence

Eleven studies met criteria for inclusion as Class III data, including all 5 of the studies in an exclusively pediatric population. All studies were classified as retrospective reviews with population sizes ranging from 29 to 436 patients (mean 102 patients). Eight of these investigations used the 50% or greater seizure reduction standard and reported a mean of 55.5% (range 38%–64.8%) responding at this level. Three articles reported on freedom from seizures at 1 year with a mean of 9.6% (range 6.9%–13%). The mean minimum follow-up in this group of studies was 11.2 months (range 3–24 months).

The largest study of the group, by Elliott et al.,[10] reviewed a single-surgeon experience with a mixed adult/pediatric population with up to 11 years of follow-up. They demonstrated significant reduction in seizure episodes with 90% or greater achieved in 22.5%, 75% or greater in 40.5%, 50% or greater in 63.75%, and less than 50% improvement in 36.25%. On multivariate analysis, focal, eloquent epilepsy was found to be a positive predictor of successful seizure control, whereas the presence of an underlying neuronal migration disorder was found to be a negative predictor.

Two other studies attempted to identify predictors of success by utilizing univariate and multivariate analysis. Ghaemi et al.[15] retrospectively reviewed 144 patients and a minimum of 2 years of follow-up data. They demonstrated seizure freedom in 6.9% and a 50% or greater seizure reduction in 61.8%. On multivariate analysis, 3 factors were found to independently correlate with successful VNS treatment: age at implantation, cortical dysgenesis, and unilateral interictal epileptiform discharges. Janszky et al.[19] similarly presented data obtained in 47 consecutive patients with a minimum of 1 year of follow-up. They were able to demonstrate a 13% rate of seizure freedom, with 2 variables found to significantly predict this freedom. In univariate analysis, these included the absence of bilateral interictal epileptiform discharges and the presence of malformations of cortical development. Following logistic regression analysis, only the absence of bilateral interictal epileptiform discharges was found to correlate independently ($p < 0.01$).

In the 2 largest pediatric investigations, Elliott et al.[11] and Murphy et al.[24] studied 141 and 96 children, respectively. Both demonstrated a significant number of responders (≥ 50% seizure reduction) with 64.8% and 45%, respectively; however, Elliott et al., having greater statistical power, were able to demonstrate significance at $p < 0.0001$ in mean reduction of episodes at 58.9%. This investigation was also able to demonstrate a 41.4% rate of 75% or greater seizure reduction. Both studies also investigated possible differences in response among younger (< 12 years of age) and older (12–18 years of age) children and found no statistically reliable results. Murphy et al. also demonstrated no difference in response among long-term epileptics (> 7 years) and those with more recent onset.

Discussion

Building on the work of Bailey and Bremmer in the 1930s and Dell, Olsen, and Zanchetti in the 1950s, Dr. Jacob Zabara formulated a technology that now fills a vital role in the active management of patients with intractable epilepsy. By applying intermittent electrical current to the cervical vagus nerve, he proposed to "desynchronize" cerebral cortical activity, thereby attenuating seizure frequency. His work was followed by application in the first humans in 1988, FDA approval in 1997, and over 20 years of prospective study establishing the role of VNS in the modulation of medically refractory epilepsy.

The application of this technology over the succeeding decades has been refined by hundreds of prospective and retrospective investigations. The initial pilot studies of VNS were designed to establish efficacy and safety and succeeded in reducing seizure frequency with minimal side effects of hoarseness and neck tingling. These were followed quickly by 2 landmark RCTs by Ben-Menachem et al.[5] and Handforth et al.[17] that established the recommended therapeutic dose. Both Class I investigations supported the notion that initiating treatment with high stimulation was far more likely to achieve the goal of reduction in seizure frequency than lower-level stimulation. Both studies also provided the impetus and support for eventual FDA approval of VNS in 1997 for the adjunctive treatment of refractory epilepsy.

Where the Class I studies established potential efficacy and tolerability, the Class II studies have served to demonstrate longevity and consistency in treatment. With extended follow-up durations from 1 to 6 years, the 7 publications identified here provide strong evidence for the use of VNS in multiple epilepsy syndromes over extended periods of treatment. With large, prospectively collected data sets, the investigations of George et al.[14] and Salinsky et al.[25] have served to confirm the utility of high-stimulation VNS for increased seizure control. Ben-Menachem et al.[4] expanded the prospective application of VNS to patients with generalized seizures and Lennox-Gastaut syndrome. Ardesch et al.[1] have shown convincing data that VNS not only decreases the frequency of seizures but may also decrease seizure severity, duration, and postictal period time.

Class III studies, derived from retrospective investigations, have been shown to be far more numerous than the previous 2 classes of data, if not as immediately clinically relevant. These 11 publications demonstrate consistently positive results with continued application of VNS to increasingly diverse populations. Of all of the studies reviewed, these represented, by far, the largest data set in terms of cumulative patients evaluated. This volume of information has been used to establish trends in outcome not otherwise evident in investigations with smaller sample sizes. Focal epileptogenic foci and the presence of cortical malformations have been shown to be positive predictors of success with VNS treatment by multiple investigators, including Elliott et al.,[10,11] Janszky et al.,[19] and Ghaemi et al.,[15] but the issue of most appropriate age of implantation appears to remain subject to argument. Ghaemi et al. found younger age at initiation of treatment to be a positive predictor, whereas both Elliott et al. and Murphy et al. found no statistical correlation between younger age and positive outcome.

Conclusions

Vagal nerve stimulation is a safe and effective alternative for adult and pediatric populations with epilepsy refractory to medical and other surgical management.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Guthikonda, Connor, Nixon. Acquisition of data: Connor, Nixon. Analysis and interpretation of data: Connor. Drafting the article: Connor, Nixon. Critically revising the article: Guthikonda. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Guthikonda. Study supervision: Guthikonda.

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Brain stimulation for the treatment of epilepsy

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The treatment of patients with refractory epilepsy has always been challenging. Despite the availability of multiple antiepileptic medications and surgical procedures with which to resect seizure foci, there is a subset of epilepsy patients for whom little can be done. Currently available treatment options for these unfortunate patients include vagus nerve stimulation, the ketogenic diet, and electric stimulation, both direct and indirect, of brain nuclei thought to be involved in epileptogenesis. Studies of electrical stimulation of the brain in epilepsy treatment date back to the early 20th century, beginning with research on cerebellar stimulation. The number of potential targets has increased over the years to include the hippocampus, subthalamic nucleus, caudate nucleus, centromedian nucleus, and anterior nucleus of the thalamus (ANT). Recently the results of a large randomized controlled trial, the electrical Stimulation of the Anterior Nucleus of Thalamus for Epilepsy (SANTE) trial, were published, demonstrating a significant reduction in mean seizure frequency with ANT stimulation. Soon after, in 2011, the results of a second randomized, controlled trial—the NeuroPace RNS trial—were published. The RNS trial examined closed-loop, responsive cortical stimulation of seizure foci in patients with refractory partial epilepsy, again finding significant reduction in seizure frequency. In the present review, the authors examine the modern history of electrical stimulation of the brain for the treatment of epilepsy and discuss the results of 2 important, recently published trials, the SANTE and RNS trials.
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Key Words • **deep brain stimulation** • **epilepsy** • **electrical stimulation**

Epilepsy is a highly prevalent disorder that is a major cause of morbidity in patients throughout the world. Nearly 1% of the population suffers from epilepsy, with an annual incidence of 50/100,000 people.[40] In 60%–70% of epilepsy patients, treatment with antiepileptic medications results in seizure remission.[40] The remaining patients, in whom symptoms are refractory to medications, currently have relatively limited alternative treatment options. Perhaps the most effective option in patients with medically refractory epilepsy is resective epilepsy surgery, which involves the excision of the epileptogenic region of the brain. In patients with well-defined epileptic zones, this can offer a high likelihood of excellent long-term seizure control.[12] In medically intractable patients in whom resection fails to control seizures, or for patients who are not appropriate candidates for surgery, there are a limited number of available palliative options.[21,37,43]

Abbreviations used in this paper: ANT = anterior nucleus of the thalamus; DBS = deep brain stimulation; EEG = electroencephalography; STN = subthalamic nucleus; TLE = temporal lobe epilepsy; VNS = vagus nerve stimulation.

Recently there has been resurgence in interest in the use of brain electrical stimulation for the treatment of patients in whom all else has failed. Multiple deep brain stimulation targets have been studied, including the cerebellum, hippocampus, subthalamic nucleus, caudate nucleus, centromedian nucleus, and anterior nucleus of the thalamus[39] (Fig. 1). Technology itself has also advanced, with the development of responsive cortical stimulation systems that are able to detect seizure activity in real time and deliver direct electrical stimulation to seizure foci in response.[33] In the past year, the results of 2 large randomized, controlled trials have been published: the SANTE (Stimulation of the Anterior Nucleus of Thalamus for Epilepsy)[17] and RNS cortical stimulation trials.[33] In the present article, we review the current and future applications of electrical stimulation for the treatment of epilepsy, including the recent results of the SANTE and RNS trials.

Vagus Nerve Stimulation

In 1997, the US FDA–approved left-sided VNS for the treatment of medically refractory partial epilepsy (Fig. 2). Vagus nerve stimulation has been by far the most

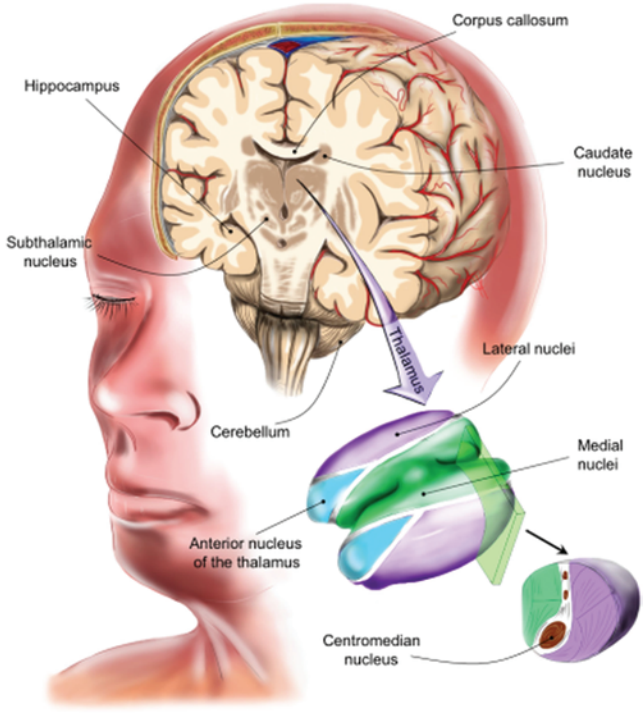

Fig. 1. Illustration demonstrating DBS targets that have been previously studied including the cerebellum, hippocampus, STN, caudate nucleus, CMN, and ANT.

prevalent method of stimulation to treat epilepsy, with more than 60,000 patients having received the implant.[15] It is presumed that stimulation of the vagus nerve results in alterations of activity in the brain, resulting in turn in a decrease in seizures. The mechanism of neuromodulation remains unclear, but it is thought that afferent signaling from the stimulated vagus nerve results in EEG desynchronization.[6,22,26]

There have been 2 randomized double-blind trials demonstrating the efficacy of VNS. In 1994, Ben-Menachem et al.[2] enrolled 114 patients with medically refractory partial epilepsy into a multicenter trial of VNS. After implantation of the stimulator, patients were randomized to receive high-frequency (treatment) or low-frequency (sham) stimulation. Three months after surgery, the investigators found a significant seizure reduction of 25% in the treatment group compared with 6% in the sham group ($p = 0.072$). A second multicenter randomized blinded trial by Handforth et al.[21] similarly randomized 196 patients (age range 13–65 years) to high- and low-frequency stimulation groups and measured seizure frequency over a 3-month period. They found that patients in the high-stimulation group had an average 28% seizure burden reduction compared with a 15% reduction in the low-stimulation group ($p = 0.04$). Although the Class I evidence supports the use of VNS only in adults and adolescents with medically refractory partial epilepsy, a recent meta-analysis[16] of Class II and III clinical studies suggests similar efficacy in children (55% reduction in seizures), as well as benefit in patients with generalized epilepsy (58% reduction in seizures). The role of VNS in palliating seizure burden appears to be expanding, although further randomized, blinded, and controlled studies are needed to confirm its efficacy with broader applications.

Deep Brain Stimulation Targets for Treatment of Epilepsy

Cerebellum

Interest in stimulating the cerebellum for epilepsy treatment began in 1941, when Moruzzi,[34] followed by Cooke and Snider,[9] discovered that electrical stimulation of the cerebellum can modify or even halt cortically induced seizures. In 1955, Iwata and Snider[24] studied hippocampal epilepsy and similarly found that cerebellar stimulation resulted in termination of induced hippocampal seizures. These findings led to animal studies of cerebellar stimulation involving various animals, seizure induction methods, stimulation parameters, and electrode locations. However, these initial studies yielded mixed results, with seizure termination not achieved in several studies.[19] The results from these early studies, including the absence of significant adverse effects, led to additional research into cerebellar stimulation in patients with medically refractory epilepsy.

After numerous small clinical studies that produced promising results,[19] Van Buren et al.[45] performed the first double-blind crossover study of 5 patients with medically intractable seizures in whom electrodes were placed on the superior surface of the cerebellum. The patients had a variety of partial and generalized seizures, with focal and/or bilaterally synchronous epileptiform discharges on EEG. In the 15–21 months following implantation of the electrodes, seizure frequency was evaluated in the hospital during three or four 4- to 6-week hospital admissions, during which 7-day periods of alternating on-and-off stimulation were used. No significant differences in seizure frequency were found between intervals. Three of the 5 patients suffered postoperative CSF leakage from the wound. Following this study, Wright et al.[56] performed a double-blind study of 12 patients with medically intractable epilepsy of various origins and clinical patterns. Stimulators were placed on the upper surface of the cerebellum, 2 cm from the midline, through suboccipital bur holes. Patients were allocated to 1 of 3 phases, lasting 2 months each, for a total of 6 months: 1) continuous stimulation alternating from one cerebellar hemisphere to the other every minute, 2) stimulation of both cerebellar hemispheres when activated by the patient, and 3) no stimulation. Data were reported for 11 of the 12 patients, and no differences in seizure frequency or severity during the stimulation periods were noted. Complications included electrode migration in 25% of the cases, wound infection in 16.6%, and mechanical failure in 8.3%. The lack of positive findings from these 2 studies ran contrary to previous clinical studies and tempered enthusiasm for this treatment.

Following the important technological advances in brain stimulation technology since the early studies of cerebellar stimulation, including the introduction of DBS systems for various diseases, Velasco et al.[48] reevaluated cerebellar stimulation for epilepsy with a randomized double-blind pilot study in 2005. They studied 5 patients with medically intractable epilepsy in whom bilateral

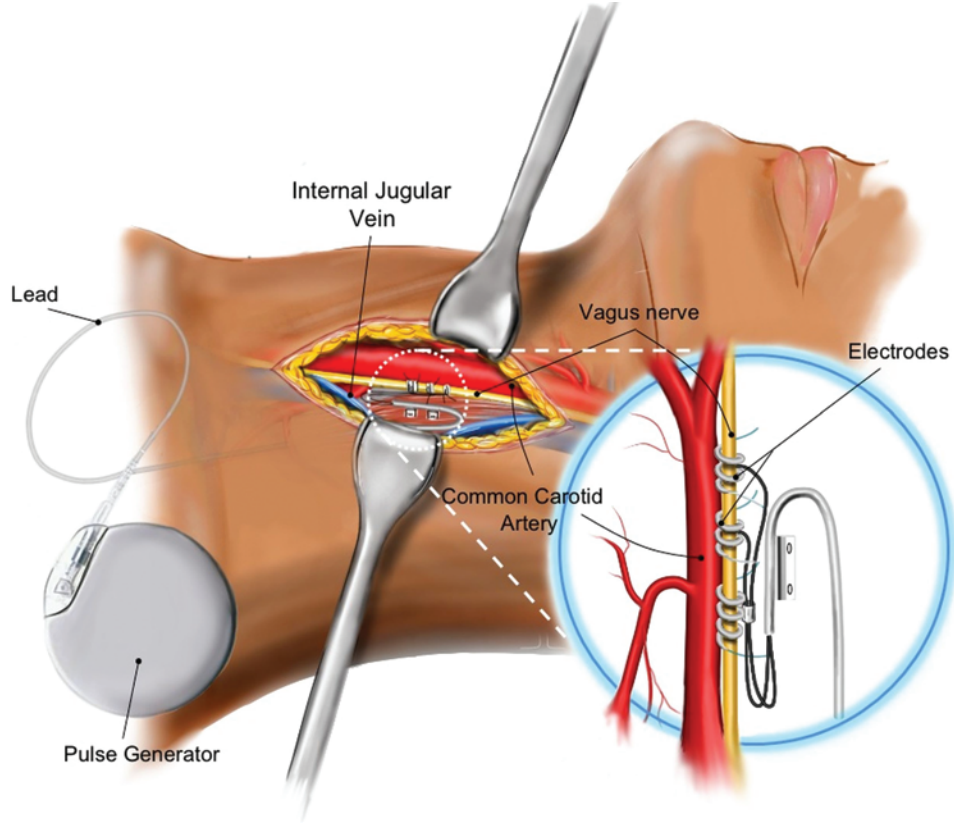

Fig. 2. Neck dissection illustrating a VNS system. There are 3 leads wrapped around the vagus nerve in a helical fashion that are connected to an implanted generator. The generator sends electrical activity to the leads that affect vagus nerve afferent fibers and, through an as-of-yet unknown mechanism, decreases the frequency of seizures in patients with partial-onset epilepsy.

4-contact plate electrodes were placed on the superomedial surface of the cerebellum through 2 suboccipital bur holes. Seizure frequency during the 3-month preimplantation phase was recorded, and postimplantation there was a 1-month sham period in which all stimulators were turned off. Thereafter, a 3-month double-blind trial began in which 3 patients received stimulation and 2 did not. After this period, seizure frequency was measured over a 6-month period during which all stimulators were turned on. Despite the small number of patients, the investigators found a significant reduction ($p = 0.023$) in generalized tonic-clonic and tonic seizure frequency. The 3 patients with stimulators turned on during the double-blind portion had a 33% reduction in seizures, compared with no change in seizure frequency in those patients with the stimulators off. During the 6-month stimulation-on period for all individuals, a mean 41% seizure rate reduction was reported. Complications included electrode migration in 3 patients (60%) and wound infection in 1 (20%).

The mechanism of antiepileptic effects of cerebellar stimulation remains unclear. Initially, it was proposed that stimulation of Purkinje cells resulted in inhibitory output from the cerebellum to the thalamocortical projections. However, histopathological study of cerebellar specimens in epilepsy patients have shown a decrease in Purkinje cell counts,[10,45] and some animal studies have suggested that stimulation inhibits, rather than excites, the Purkinje cells adjacent to the electrodes.[13,36]

Despite conflicting results from the animal studies and clinical trials, there remains considerable interest in cerebellar stimulation for the treatment of medically intractable epilepsy pending further clarification of the more precise target of stimulation and the appropriate stimulator frequency. The results of the pilot study reported by Velasco et al.[46] indicate that further clinical studies involving larger number of patients may be warranted.

Hippocampus

Patients with medically intractable mesial TLE routinely undergo surgical workups to determine if they are appropriate candidates for anteromesial temporal lobectomy[14] or selective amygdalohippocampectomy.[54] However, patients with bilateral mesial TLE, or those with unilateral mesial TLE involving a dominant hippocampus that is essential for adequate memory function, may not be candidates for resection. Moreover, although resection in TLE has proven effective, not all patients experience full relief of seizure burden, and resection is associated with small, but not trivial, risk of a new neurological deficit.[14] For these reasons, there has been interest in targeting the hippocampus for stimulation to treat mesial TLE. The potential advantages of stimulation over anteromesial temporal lobe resection include the reversibility of stimulation, as well as a theoretically decreased risk of inducing memory, language, and visual deficits. The postulated mechanism for the effect of hippocampal stimulation re-

mains unclear, but some have suggested that activation of the perforant pathways results in polysynaptic inhibition of the epileptogenic neurons residing in CA1–4.[50]

Velasco et al.[50] have explored the use of hippocampal stimulation in the treatment of mesial TLE in patients in whom subdural or depth electrodes were implanted to determine seizure foci before a temporal lobectomy. In the study period of 2–3 weeks during which antiepileptic drugs were discontinued, the authors found that in 7 patients who received continuous stimulation of the hippocampal formation or gyrus, no clinical seizures were noted; furthermore, the number of interictal EEG spikes recorded from the hippocampal foci was overall decreased by 60% after 5–6 days. Further studies by Vonck et al.,[53] and again by Velasco et al.,[47] supported these findings. Tellez-Zenteno and colleagues[44] performed a small double-blinded randomized crossover trial in 4 patients with unilateral mesial TLE in whom resection was contraindicated due to risks to memory. In each patient, 1 electrode was placed along the longitudinal axis of the affected hippocampus, via a posterior bur hole. Patients underwent randomized 1-month on- or off-stimulation periods over 6 months, during which blinded investigators measured seizure frequency and performed neuropsychological testing. The investigators found that stimulation produced a median reduction of seizures of 15%, but this percentage did not reach significance in the study sample. There was no difference in secondary outcomes, with stimulation compared with no stimulation, in terms of quality of life, mood, and seizure severity. A second small, double-blind randomized crossover study of bilateral mesial TLE in just 2 patients[31] also failed to replicate the promising results of the earlier nonblinded clinical studies. In this study, bilateral electrodes were placed along the axis of the hippocampus. Following a 3-month baseline period, patients underwent randomized 3-month periods of receiving stimulation or not receiving stimulation while blinded investigators measured seizure frequency and neuropsychological outcomes. The investigators found a 33% reduction in seizures during the on-stimulation phase compared with the off phase.

Randomized controlled double-blind trials of a larger number of patients are needed to better clarify the role, if any, of hippocampal stimulation in the treatment of TLE. Currently, the METTLE (http://clinicaltrials.gov/ct2/show/NCT00717431) and the CoRaStir (http://clinicaltrials.gov/ct2/show/NCT00431457) randomized controlled trials are among the those underway to clarify the role of this treatment modality.[25] The METTLE trial is a multicenter parallel-group double-blind randomized controlled trial enrolling adults with uni- or bilateral mesial TLE, including those who may be candidates for resection and those who are not. These patients undergo hippocampal electrode implantation and are randomized to a stimulation or no-stimulation group. At the end of a 7-month follow-up period and outcome assessment, patients are then offered electrode removal, surgical therapy, or medical therapy based on best evidence. Primary and secondary outcomes will include seizure frequency, cognition, mood, and quality of life. The CoRaStir trial will randomize adults with TLE into 1 of 3 treatment arms: amygdalohippocampectomy, hippocampal electrode with stimulation, or hippocampal electrode without stimulation. Investigators will report outcomes in seizure frequency, neuropsychological testing, and quality of life.[25]

Subthalamic Nucleus

The role of the basal ganglia in epilepsy has been previously explored in a number of experiments. Injection of γ-butyric-acid agonists and lesioning of the substantia nigra suppress seizure activity in many animal models of epilepsy.[20] The STN has glutamatergic efferents to the substantia nigra and modulates its inhibitory output. This anatomical property, coupled with the growth of experience with STN DBS in diseases such as Parkinson disease, led Vercueil et al.[51] to perform STN DBS in a rat model of epilepsy. Bilateral high-frequency STN DBS was found to suppress ongoing spontaneous absence seizures in rats and suggested its clinical application in humans.

In 2001 Benabid et al.[3] were the first to report a series of 3 patients with medication refractory epilepsy who were implanted with STN DBS. One patient had focal cortical dysplasia, the second had myoclonic epilepsy, and the third (in whom surgical therapy failed) had bilateral frontal epilepsy. All 3 patients were reported to have significant reduction in seizure frequency with stimulation, 83% and 50% in the first 2 patients. The percentage of reduction in the third patient was not reported.

Since then several studies of patients have demonstrated mixed results from STN DBS for epilepsy.[4,5,41,52,55] Chabardès et al.[5] reported a series of 5 patients with different epilepsy subtypes treated with STN stimulation. Three patients had partial seizures and had a 67%–80% reduction in seizure frequency, whereas the others, 1 with myoclonic epilepsy and 1 with Dravet syndrome, witnessed little to no improvement. In a recent series of 5 patients with refractory myoclonic epilepsy,[55] STN/substantia nigra DBS resulted in a 30%–100% reduction in seizure frequency in all patients. Interestingly, 4 of the 5 patients had an additional set of electrodes implanted in the ventral intermediate nucleus, but stimulation there failed to produce any therapeutic effect. The published clinical reports indicate that STN DBS may be a promising therapeutic target in patients with certain forms of epilepsy, but both larger series and more rigorous clinical trials are needed to determine the role of STN DBS in epilepsy.

Caudate Nucleus

The role of the caudate nucleus in modulation of seizure activity has been suggested by animal studies demonstrating reduced hippocampal spike frequency and amplitude with caudate stimulation.[28] In several series of patients reported by Sramka and associates[42] and Chkhenkeli and collaborators,[7,8] stimulation of the caudate nucleus was performed for treatment-resistant epilepsy. In a 1997 study of 38 patients, Chkhenkeli and Chkhenkeli[7] showed that low-frequency stimulation (4–6 Hz) led to a decrease in interparoxysmal activity and focal discharges in the neocortical and medial temporal epileptic foci, as well as abrupt cessation of spreading and generalized discharges. Later, in 2004, Chkhenkeli and colleagues[8] showed that low-frequency caudate stimula-

tion reduced the frequency of generalized, complex, and secondary generalized seizures and suppressed subclinical epileptic afterdischarges. More studies are needed to determine if the caudate nucleus represents a viable epilepsy DBS target.

Centromedian Nucleus

The CMN is thought to help regulate structures involved in the genesis of generalized seizures through widespread connections to various cortical areas including mesial temporal lobe structures.[32] In 1987 Velasco et al.[49] reported on a series of 5 patients with generalized or multifocal refractory seizures who underwent bilateral CMN DBS. They found a substantial reduction in the frequency of seizures, both clinically and on EEG. A follow-up study in 2006[46] of 13 patients with Lennox-Gastaut syndrome showed an overall seizure frequency reduction of 80% at 18 months postimplantation, significant functional improvement, and no reported side effects. The most severely affected patients seemed to respond the most to stimulation.

Fisher et al.[18] performed a double-blind crossover pilot study of CMN stimulation in 7 patients with intractable epilepsy. The patients underwent 3 month-long periods with or without stimulation and a 3-month washout period in between. There was a 30% mean reduction in frequency of generalized tonic-clonic seizures when the stimulator was on compared with a decrease of 8% when it was off. There were no reported treatment side effects. Treatment differences were not significant.

Anterior Nucleus of the Thalamus

The ANT represents an attractive stimulation target due to its widespread thalamocortical projections. Early studies in both animal models of epilepsy[27] and in humans with refractory epilepsy[35] had demonstrated that lesioning of the ANT can decrease seizure frequency and duration. It was not until after the advent of DBS that the first human ANT DBS for epilepsy study was published in 1980 by Cooper et al.[11] In 2002, Hodaie et al.[23] published the results of a series of 5 patients with medically refractory epilepsy who underwent bilateral ANT electrode placement. There was an overall mean seizure reduction of greater than 50%. However, the decrease in seizure frequency began immediately after electrode implantation and before stimulation began. It was therefore not clear whether the seizure reduction was due to the implantation of the electrodes themselves or because of stimulation or both. Subsequent published studies of small series of patients with ANT implants showed similar results.[1,29,30,38]

In 2010 the highly anticipated results of the SANTE trial were published.[17] The SANTE trial was the first large, multicenter, double-blind, randomized trial that examined the effects of ANT DBS in patients with intractable epilepsy. A total of 110 patients underwent bilateral electrode implantations in the ANT. One month after implantation, the patients were then randomized to either a stimulation group or a no-stimulation group for a 3-month "blinded" phase. This was followed by a 9-month open-label phase in which all patients had their stimulators turned on and stimulation parameters were optimized to minimize adverse events. Long-term follow-up was achieved in 99 patients at 13 months and 81 patients at 25 months. The primary outcome assessed was monthly seizure rate. Secondary outcomes included the Liverpool Seizure Severity Scale, Quality of Life in Epilepsy Scale, and neuropsychological assessment.

At the end of the 3-month blinded phase, there was a 40.4% decrease in median seizure frequency in the stimulated group compared with a 14.5% decrease in the control no-stimulation group ($p = 0.0017$). That the control group also had a decrease in seizure frequency is consistent with studies mentioned previously showing an implantation effect. This effect alone, however, does not explain the significant difference between the stimulation and control group and suggests stimulation did indeed have an effect. Interestingly, patients with seizures originating from one or both temporal lobes had a significant difference in median seizure reduction in the stimulation group compared with the control group (44.2% and 21.8%, respectively; $p = 0.025$), while patients with seizures originating from the frontal, parietal, or occipital lobe did not.

During the long-term follow-up there was a 41% decrease in median seizure frequency at 13 months and 56% decrease at 25 months. Fourteen patients were seizure free for at least 6 months during the entire study. Nine patients had an increase in median seizure frequency at 25 months. The most common adverse event was paresthesias, reported in 18.2% of participants, which tended to occur during the 1st month of implantation. Depression and memory impairment occurred in significantly more people in the stimulation group during the blinded phase ($p = 0.0162$ and 0.0316, respectively), although most were transient events and resolved during term follow-up.

The SANTE trial demonstrated the overall effectiveness of ANT stimulation as a palliative measure for reducing seizure frequency in patients in whom epilepsy is refractory to medical therapy. In addition, there were 14 patients who were seizure free for at least 6 months during the study period, indicating that some patients may benefit from ANT stimulation more than others. Further study of the optimal patient selection criteria for this promising procedure is indicated.

Responsive Stimulation

An important recent development in the ongoing development of brain stimulation as a viable therapy for epilepsy is the advent of "open loop" or responsive cortical stimulation. Traditional DBS involves the use of chronic, continuous stimulation of a target, so-called closed-loop stimulation. Responsive stimulation first involves implantation of subdural or depth electrodes in a brain target area of interest (Fig. 3). The electrodes are then connected to a small device implanted subcutaneously in the individual. Unlike traditional closed-loop systems, the electrodes have both a stimulation and detection function. Electrocorticographic activity at the target is continuously monitored and recorded by the implanted computer. When abnormal electrocorticographic activity is detected, electrical stimulation is delivered with the goal of dis-

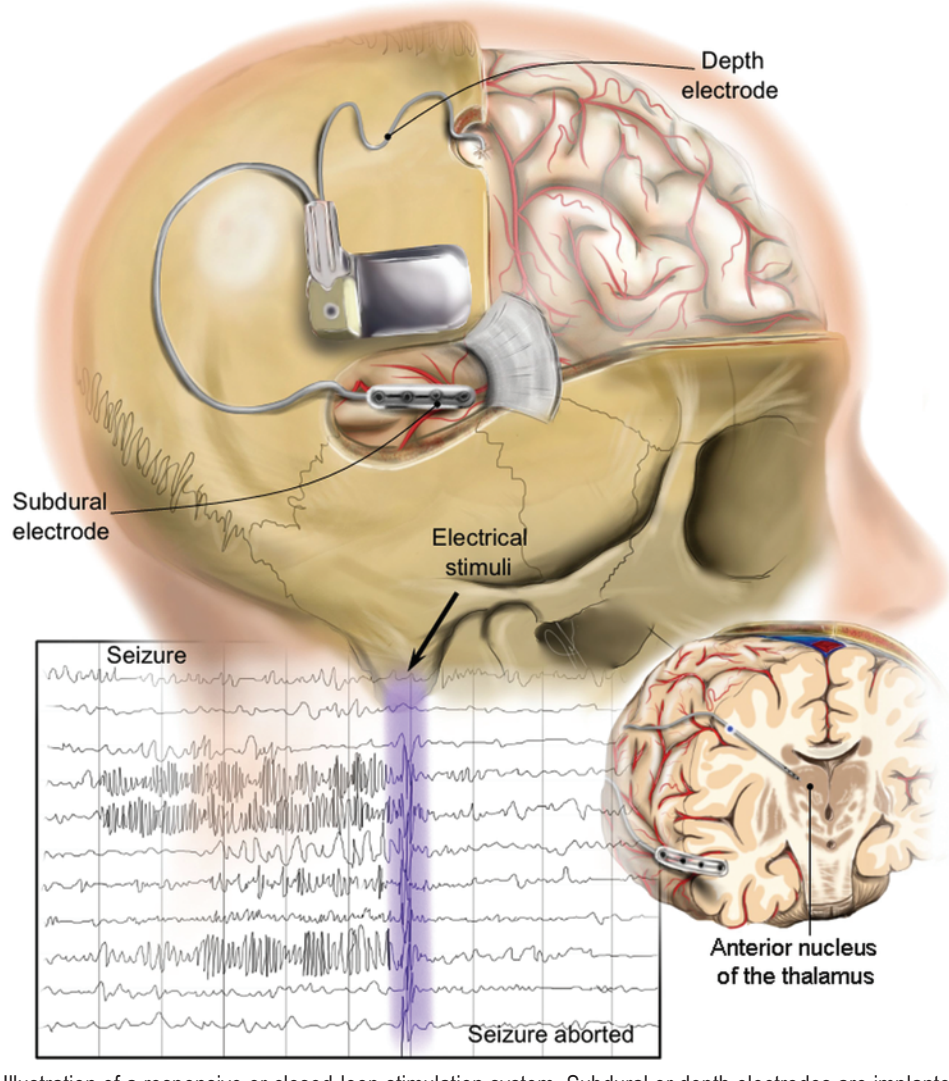

Fig. 3. Illustration of a responsive or closed-loop stimulation system. Subdural or depth electrodes are implanted into or adjacent to seizure foci. The electrodes are connected to a neurostimulator implanted in the patient's skull. When electrical activity that heralds the onset of a seizure is detected, electrical stimulation is sent to the site of lead implantation, disrupting the abnormal electrical activity and preventing the seizure.

rupting the abnormal activity. Recently, a responsive cortical stimulation system (RNS System, NeuroPace) was studied in a large, multicenter, double-blind, randomized, controlled trial for patients with refractory partial-onset seizures, the results of which were published in 2011.[33]

In 191 adults with refractory partial-onset seizures, either subdural or depth electrodes were implanted at 1 or 2 prespecified seizure foci. The patients were randomized 1 month later into either a sham-stimulation group or a treatment group. There was a 1-month, patient-blinded, postimplantation stimulation optimization period during which the treatment group, but not the sham group, had their stimulators turned on and optimized. Both groups then entered a 3-month blinded evaluation period, in which the treatment group underwent stimulation, but not the sham group. Patients in the sham group then had their stimulators turned on, and all participants entered an open-label period over 84 weeks. The primary end point studied was the difference in mean seizure frequency reduction between the treatment and sham groups compared with their baseline preimplantation seizure frequency. Multiple secondary end points were studied, including neuropsychiatric end points and quality of life measures.

During the 1st month after implantation, there was a decrease in mean seizure frequency in both the sham and treatment groups, similar to the effect seen in the SANTE trial that was attributed to an "implantation effect."[17] Because many patients in the RNS trial solely had subdural electrodes implanted, rather than depth electrodes, it is unlikely that this initial reduction in seizures, in the absence of stimulation, was due to a microlesioning effect. It is possible that there was an initial placebo effect, as the patients all knew they had electrodes implanted. Over the rest of the blinded evaluation period, a difference in seizure reduction in the treatment group compared with the sham group became more apparent, with the treatment group having 27% fewer days with seizures compared

TABLE 1: Large randomized controlled trials of brain stimulation

Authors & Year	No. of Patients	Target	Seizure Frequency Reduction Group	
			Treatment	Sham
Ben-Menachem et al., 1994	114	VNS	25%	6%
Handforth et al., 1998	196	VNS	28%	15%
Fisher et al., 2010	110	ANT	40.4%	14.5% (median)
Morrell et al., 2011	191	direct-seizure foci	37.9%	17.3%

with just a 16% reduction in the sham group ($p = 0.048$). Over the entire blinded evaluation period, there was a 37.9% reduction in mean seizure frequency in the treatment group compared with a 17.3% reduction in the sham group ($p = 0.012$). Of 102 patients who were followed up at 2 years during the open-label period, 46% had at least a 50% reduction in their mean seizure frequency. Both sham and treatment groups had similar improvements in secondary outcome measures, including quality of life, at the end of the blinded evaluation period, possibly due to close follow-up and consistent epilepsy care or a placebo effect. However, the treatment group had greater improvements at 1 and 2 years into the open-label period in verbal functioning, visuospatial ability, and memory ($p < 0.05$). There were no significant differences in adverse events between the groups.

The responsive cortical stimulation trial represents a promising potential approach for the treatment of epilepsy and potentially for other disorders, such as Tourette syndrome, in which practitioners can simultaneously monitor and tailor stimulation parameters to modulate abnormal brain electrical activity. More study of the advantages and disadvantages of open-loop systems is needed.

Conclusions

Electrical stimulation of the brain in the treatment of epilepsy has progressed significantly over the past several decades. Important developments include the completion of rigorous clinical trials (Table 1) testing several different stimulation targets for epilepsy control, as well as advances in brain stimulation technology and hardware, including smart, open-loop systems that deliver stimulation in response to recorded pre-epileptic activity in an attempt to stop seizures before they occur, in real time. Published clinical trials of brain stimulation for epilepsy have been primarily restricted to the subset of patients with medication-refractory epilepsy that is also refractory to, or not deemed appropriate for, treatment with established epilepsy surgery techniques. While statistically significant reductions in seizures have been observed using several different stimulation techniques, including VNS, anterior thalamic stimulation, and RNS, this effect is currently only palliative and does not approach efficacy comparable with that seen with resection in appropriately selected patients. Nonetheless, current limits in the efficacy of antiepileptic medications and epilepsy surgery, combined with the substantial number of patients who continue to suffer from uncontrolled epilepsy, motivate epilepsy researchers to continue to explore brain stimulation as an alternative therapy. The promising results of the aforementioned studies on brain stimulation further drive interest in refining brain stimulation for epilepsy. More research is needed to determine optimal stimulation targets and techniques, as well as to determine which epilepsy patients may benefit the most from this technology.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Yoshor. Acquisition of data: Fridley, Thomas. Drafting the article: Fridley, Thomas. Critically revising the article: Fridley, Thomas. Administrative/technical/material support: Cruz Navarro. Illustrations: Cruz Navarro.

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Comparison of seizure control outcomes and the safety of vagus nerve, thalamic deep brain, and responsive neurostimulation: evidence from randomized controlled trials

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Epilepsy is a devastating disease, often refractory to medication and not amenable to resective surgery. For patients whose seizures continue despite the best medical and surgical therapy, 3 stimulation-based therapies have demonstrated positive results in prospective randomized trials: vagus nerve stimulation, deep brain stimulation of the thalamic anterior nucleus, and responsive neurostimulation. All 3 neuromodulatory therapies offer significant reductions in seizure frequency for patients with partial epilepsy. A direct comparison of trial results, however, reveals important differences among outcomes and surgical risk between devices. The authors review published results from these pivotal trials and highlight important differences between the trials and devices and their application in clinical use.
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Key Words • epilepsy • seizure • deep brain stimulation • neuromodulation • responsive neurostimulation • vagus nerve stimulation

Epilepsy affects nearly 1 in 100 people, leading to substantial morbidity, mortality, and economic burden.[2,17,18] Up to one-third of these patients are not helped by antiepileptic medications.[17,18] For patients with medically refractory epilepsy, a potentially curative option is resection of the epileptic foci when they can be clearly delineated and safely resected.[27] However, many patients are not suitable candidates for resection, and morbidity exists for surgery.[3,16] Because of this, there is a substantial need for additional treatment modalities.

Electrical stimulation of the nervous system is a rapidly evolving treatment for refractory epilepsy, offering a reversible, adjunctive therapeutic option for patients who are otherwise not surgical candidates. Therapeutic stimulation can occur directly via DBS or indirectly via stimulation of peripheral nerves. Three modalities of stimulation now have Class I evidence supporting their use: VNS, DBS of the ANT, and RNS. This review will examine the evidence for each treatment modality and delineate which sets of patients might benefit most from each.

Abbreviations used in this paper: AED = antiepileptic drug; ANT = anterior nucleus of the thalamus; CE = Conformité Européenne; DBS = deep brain stimulation; IPG = implantable pulse generator; RNS = responsive neurostimulation; SANTE = stimulation of the anterior nucleus of the thalamus for epilepsy; VNS = vagus nerve stimulation.

Vagus Nerve Stimulation

The VNS modality is the only US FDA– and CE Mark–approved stimulation therapy for epilepsy. The device consists of pliable, spiral-shaped electrodes that wrap around the vagus nerve and an IPG that is implanted below the clavicle and connected to the electrodes with subcutaneously tunneled wires (Fig. 1).[10] The left vagus nerve is typically used due to concerns about inducing bradycardia or other arrhythmias when stimulating the right vagus, although recently reports of successful right-sided VNS have been published.[22]

The vagus nerve is largely afferent (approximately 80%) and is composed predominantly of unmyelinated C fibers.[10] These fibers project to the nucleus tractus solitarius in the brainstem, which in turn projects widely to other areas within the brainstem and to the cortex. It is presumably by these broad neuromodulatory influences that VNS exerts its antiseizure effect. Nevertheless, the exact mechanism by which VNS reduces seizure frequency is unknown, although studies have implicated a variety of neurotransmitters, such as noradrenaline[15] and γ-aminobutyric acid.[1]

There have been 2 randomized, double-blind clinical trials investigating the efficacy of VNS, titled EO3[26] and EO5,[11] and both were funded by the manufacturer of the VNS device, Cyberonics, Inc. In both trials, patients were randomized to receive either typical VNS (denoted

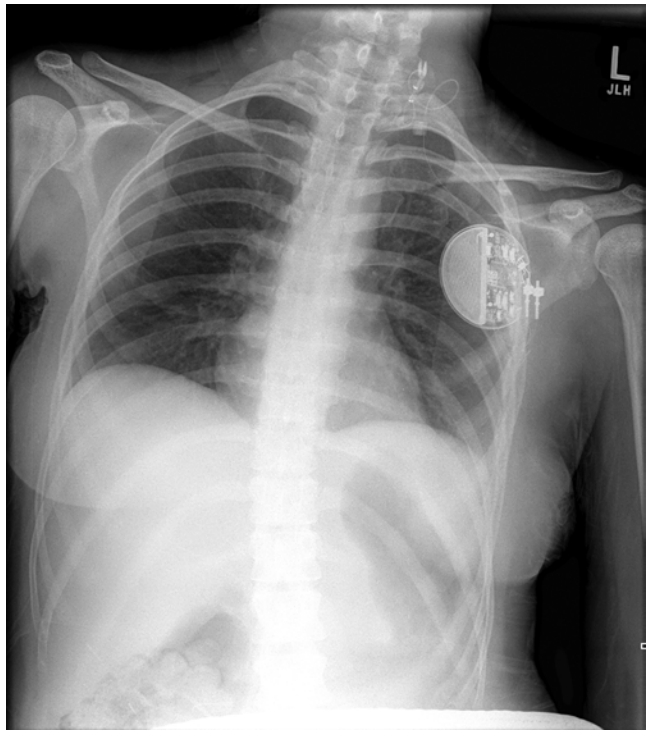

Fig. 1. Implanted VNS. This chest radiograph shows an implanted VNS system, with the IPG in the left chest, and the cuff electrode wrapped around the left vagus nerve within the neck.

"high") or an active, low-frequency control VNS (denoted "low") (Fig. 2). The patients remained on AEDs throughout the trial. High VNS consisted of a 20- to 50-Hz stimulation frequency, "on" times of 30–90 seconds, "off" times of 5–10 minutes, and the ability to activate the VNS system manually with an external magnet. The low VNS (control) group had stimulation frequencies of 1–2 Hz, "on" times of 30 seconds, "off" times of 1–3 hours, and no ability to activate the device manually.

After approximately 3 months of treatment (12–16 weeks), both trials showed significant reductions in seizure frequency compared with patient baselines (24.5% and 27.9%, respectively; Table 1). This is compared with the low-stimulation groups, which had reductions of 6.1% and 15.2%, respectively. The proportion of patients experiencing a reduction of ≥ 50% in their seizures at this same 3-month time point was between 23.4% and 31% (Table 1), again compared with 13% and 15.7% in the low-stimulation groups, respectively.

The inclusion criteria were similar between the 2 trials. Both required patients to have ≥ 6 seizures per month, be ≥ 12 years old, use at most 3 AEDs, and have medically refractory seizures. The EO3 trial, however, required seizures to be "predominantly partial," whereas EO5 required that the 6 minimum seizures all be partial, but permitted other seizure types in excess of the minimum. The EO5 trial also added an upper age limit of 65 years, limited time between seizures to a maximum of 21 days, and required that AEDs be at steady state before the patient's induction into the trial.

Adverse events were common in both high- and low-stimulation groups, although only voice alteration and dyspnea were significantly increased in the high versus low groups. Overall, 66.3% of actively treated patients experienced voice alteration; 45.3% had cough; 34.7% had pharyngitis; 28.4% had pain; 25.3% had dyspnea; 24.2% had headache; 17.9% had dyspepsia, vomiting, and paresthesias; 14.7% had nausea; 12.6% had accidental injury; and 11.6% had fever and infection (Table 2).

Both Class I trials were short term, lasting only 12–16 weeks. After the trials were unblinded, the patients were continually followed, and the results seemed to improve over time. After 1 year, for example, patients in the EO5 study experienced a 45% reduction in seizure frequency, and 35% had a reduction of ≥ 50% in seizures.[7] In the EO3 trial, those patients who were randomized initially to high stimulation had a reduction of 43.0%, whereas those switched from low to high stimulation experienced a 27.5% reduction.[9] Nevertheless, these unblinded extensions do not constitute Class I evidence.

Anterior Nucleus Stimulation

The ANT projects to both the frontal and temporal lobes and is part of the classic circuit of Papez.[24] Because of this integral role in the limbic system, an area intimately associated with epilepsy, many groups have attempted stimulating the anterior nucleus in humans in an effort to suppress seizures, with varying degrees of success.[5,6,12,14,19,21]

The SANTE trial (ClinicalTrials.gov NCT00101933) was a double-blind, randomized, prospective clinical trial of DBS of the ANT.[8] It began in 2005, and results were published in 2010. It was sponsored by Medtronic, Inc. After accruing patients and determining their baselines for 3 months, all patients were implanted with a Model 7428 Kinetra Neurostimulator and Model 3387 DBS leads (both from Medtronic) (Figs. 3 and 4). One month after implantation, patients were randomized to active treatment, with stimulation parameters of 5-V pulses at 145 Hz, with 1 minute "on" and 5 minutes "off," versus 0-V pulses with identical frequency and duty cycle in the control group (Fig. 2).

Inclusion criteria for the SANTE trial were similar to the VNS trials that preceded it: age range 18–65 years, partial seizures, ≥ 6 seizures per month, and medically refractory epilepsy (defined as at least 3 failed AEDs). Important differences are the minimum age of 18 years, rather than 12 years used in the VNS trials, and a maximum of 4 AEDs used concurrently at baseline (compared with 3 in the VNS trials). The SANTE trial also excluded patients with > 10 seizures per day and patients with brain tumors, neurodegenerative diseases, psychogenic seizures, or IQ < 70. If the prospective SANTE patients had VNS devices, these were removed at the time of DBS implantation.

After a follow-up of 3 months, treated patients had a median decrease in seizures of 40.4%, compared with 14.5% in the control group. As with the VNS patients, the SANTE patients were then unblinded and followed for an additional time period. After 2 years, the treated SANTE patients (in this unblinded cohort) had a 56% median reduction in seizure frequency, and 54% of patients had a reduction in seizures of ≥ 50% (Table 1).

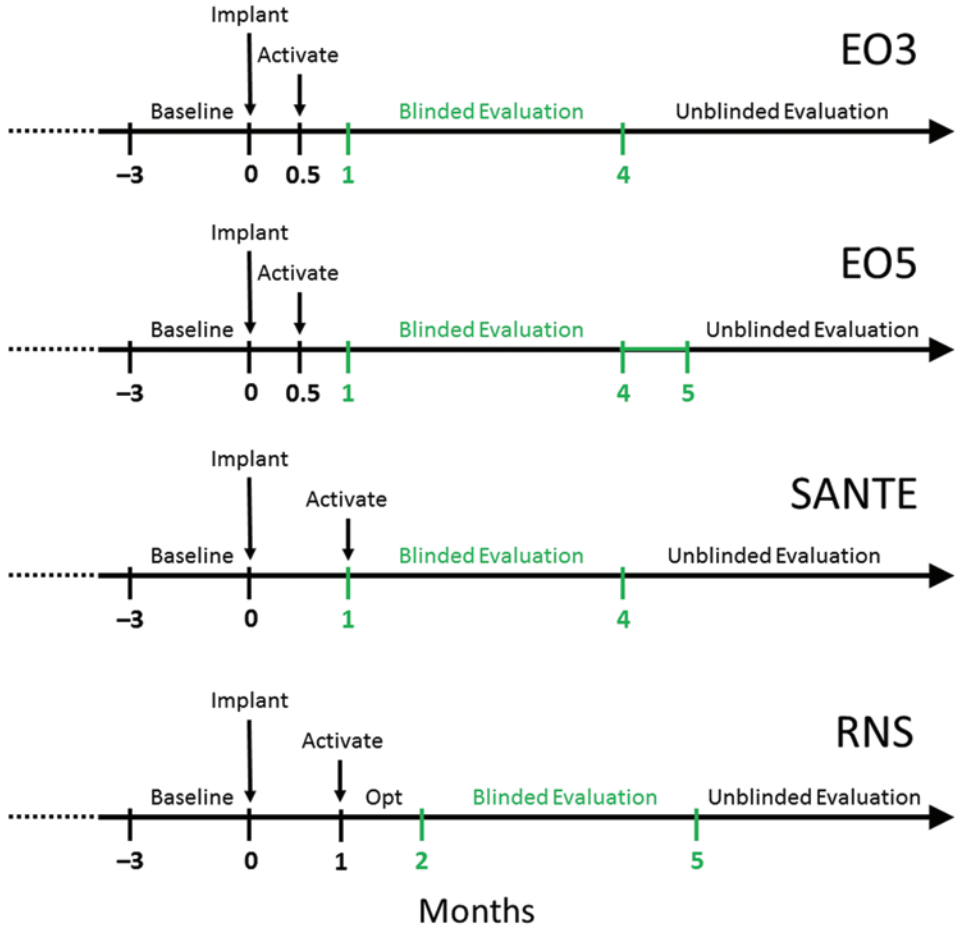

Fig. 2. Trial timelines. Timelines for the 4 randomized clinical trials are shown. All had 3-month baseline periods. In the EO3 and EO5 trials, VNS devices were implanted, activated 2 weeks later, and then investigators waited 2 more weeks before beginning the definitive trial. The blinded evaluation period of EO3 lasted 3 months, whereas the evaluation period of EO5 was variable, from 3 to 4 months. In the SANTE trial patients received the implant after 3 months of baseline evaluation, and then waited 1 month before beginning the blinded period. In the RNS trial, because it took time to train the devices to recognize seizures, a 1-month period (1 month after implantation) was used for optimizing device parameters (Opt). The blinded evaluation period was thus started 2 months postimplant, lasting 3 months.

Over the course of the 1st year, adverse events directly related to the device in the SANTE trial included paresthesias in 18.2%, implant site pain in 10.9%, implant site infections in 9.1%, and lead replacement in 8.2% of patients. Note that these frequencies include the unblinded portion of the trial—the adverse events in the blinded portion are displayed in Table 2. Adverse events that were significantly different between groups in the blinded phase were depression (14.8% of treated patients) and memory impairment (13.0%).

TABLE 1: Randomized controlled trials of VNS compared with other stimulation-based therapies*

Study	No. Patients (no. in active group)	% w/ Seizure Reduction, Blinded (95% CI)	% w/ Seizure Reduction, 1 Yr	% Responder Rate, Blinded	% Responder Rate, 1 Yr	Regulatory Approval	
						FDA	CE Mark
VNS						yes	yes
EO3	114 (54)	24.5 (14.1–34.9)	43	31			
EO5	196 (94)	27.9 (21.0–34.8)	45	23.4	35		
thalamic DBS—SANTE	109 (54)	40.4 (NR)	41	NR	43	†	yes
cortical stimulation—RNS	191 (97)	37.9 (27.7–46.7)	NR	29	43	†	†

* Seizure reduction is defined as change in actively treated patients compared with their baseline seizure frequency. Responder rates are defined as a ≥ 50% reduction in seizure frequency experienced in actively treated patients. The ≥ 50% responder rate is not reported in the SANTE trial, although it was not significantly different from the untreated group. NR = not reported.

† Pending review.

TABLE 2: Adverse events across trials*

Adverse Event	VNS		Thalamic DBS (SANTE)	Cortical Stimulation (RNS)
	EO3	EO5		
hoarseness/voice change	37.2	66.3	—	—
coughing	7.4	45.3	—	—
nasopharyngitis	11.1	34.7	1.9	—
pain	5.6	28.4	—	0.5
dyspnea	5.6	25.3	—	—
headache	1.8	24.2	3.7	2.6
paresthesia	5.6	17.9	9.3	0.5
dyspepsia	—	17.9	—	—
vomiting	—	17.9	—	—
depression	—	—	14.8	1.1
nausea	—	14.7	—	—
memory impairment	—	—	13.0	0.5
injury (accidental)	—	12.6	1.9	—
fever	—	11.6	—	—
infection	—	11.6	—	—
anxiety	—	—	9.3	—
partial seizures w/ generalization†	—	—	9.3	—
complex partial seizures†	—	—	9.3	4.3
confusional state	—	—	7.4	—
influenza	—	—	5.6	—
simple partial seizures†	—	—	5.6	2.2
anticonvulsant toxicity	—	—	5.6	—
dizziness	—	—	5.6	—

* All reported adverse events occurring in ≥ 2.5% of patients during the blinded evaluation period. — = data not provided.

† New, increased, or exacerbated.

Responsive Neurostimulation

The RNS device is designed to detect seizures as they start and then stimulate the seizure focus to abort the propagation. This idea has empirical evidence supporting its feasibility.[20] Responsive neurostimulation is a closed-loop system, in which subdural and depth electrodes record electrographic activity and trigger bursts of stimulation when a seizure is detected, in the hope of terminating the seizure before it is clinically apparent (Fig. 3).

In the RNS System Pivotal Trial (ClinicalTrials.gov NCT00264810), 191 patients were implanted with the NeuroPace RNS system (NeuroPace, Inc.) following a 3-month baseline period.[23] Two months after surgery (and after optimizing seizure detection parameters), patients were randomized to responsive stimulation or pure detection of seizures without stimulation. Both groups were followed for 12 weeks in this blinded period (Fig. 2).

Inclusion criteria were age 18–70 years, partial seizures, medically refractory epilepsy (failure of ≥ 2 AEDs), 3 or more seizures per month (on average), and an EEG workup showing 1 to 2 epileptogenic regions. Over the 3-month follow-up period, stimulated patients reported a decrease in seizure frequency of 37.9%, versus 17.3% in the sham-treated group. In addition, 29% of patients reported a decrease in seizures of ≥ 50%, although 27% of sham-treated patients had this responder rate as well (Table 1).

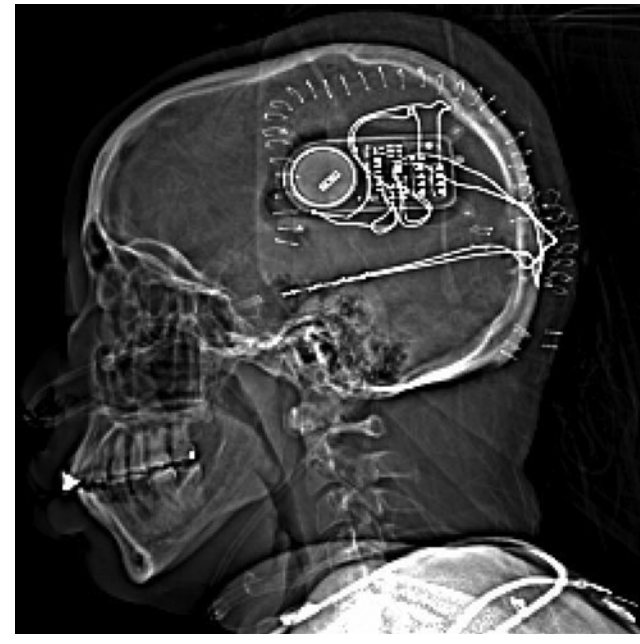

Fig. 3. NeuroPace RNS Device. This scout CT scan shows the closed-loop RNS device implanted in a patient with medically refractory epilepsy. The IPG is fixed in the skull, with penetrating depth electrodes extending into the hippocampi bilaterally. Surgical staples can also be seen surrounding the scalp flap. Image provided by Dr. Rosana Esteller, NeuroPace, and Dr. Robert Gross, Emory University.

As in the VNS trials and the SANTE trial, patients were followed continually after the end of the blinded phase. The RNS-treated patients continued to benefit from the device at 1 and 2 years postimplant, with 43% and 46%, respectively, achieving a ≥ 50% reduction in seizures (Table 1).

During the blinded evaluation period, there was no difference between the treatment and sham-treated groups in terms of reported adverse events. Nevertheless, when compiled over the study's entire 1st year, adverse events included incision site infections in 5.2% of patients, headache in 10.5%, dysesthesia in 6.3%, increased complex partial seizures in 5.8%, increased tonic-clonic seizures in 4.7%, memory impairment in 4.2%, depression in 3.1%, and dizziness and paresthesias in 2.6%. Adverse events that occurred strictly within the blinded phase are displayed in Table 2.

Choice of Therapy

Only VNS is approved by the FDA and therefore currently remains the primary choice of most US providers as an adjunctive treatment for refractory epilepsy (Table 1). Nevertheless, both NeuroPace and Medtronic have applied for FDA approval of the RNS System and DBS of the ANT, respectively. NeuroPace applied in July 2010 and is awaiting a panel meeting and recommendation before the FDA takes action. The FDA panel has convened and voted to approve Medtronic's ANT DBS device. However,

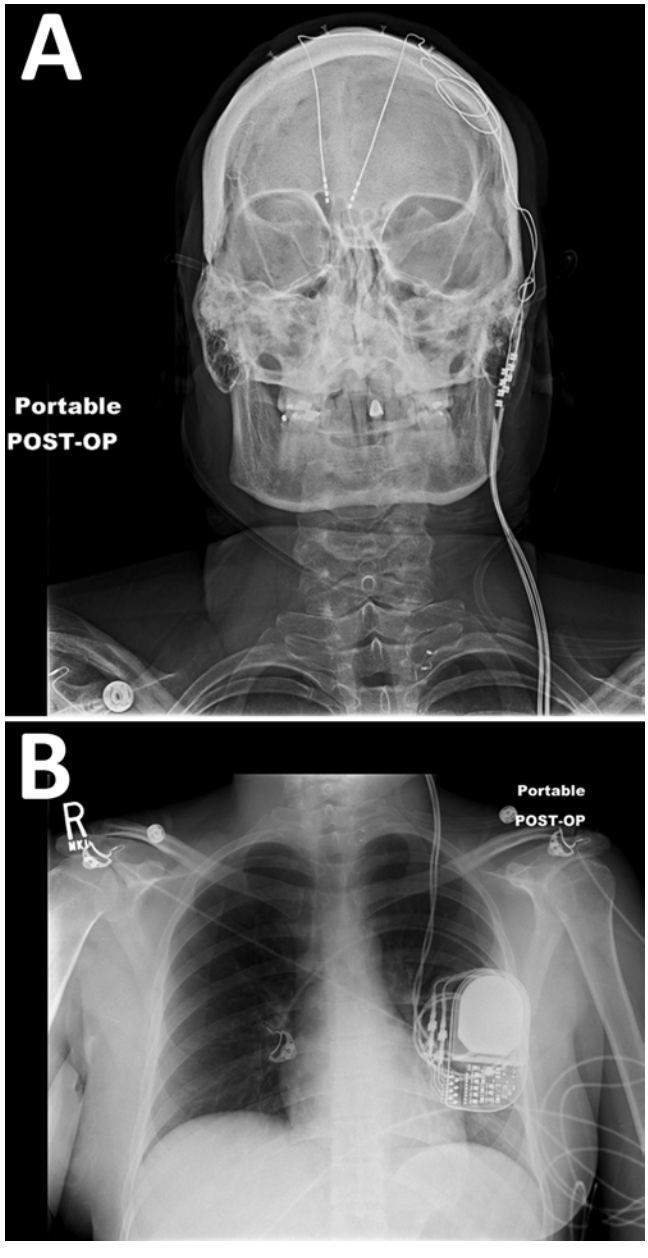

Fig. 4. Implanted DBS for ANT. **A:** This anterior-posterior head radiograph shows bilateral DBS electrodes implanted within the ANT. The connectors are tunneled subcutaneously within the left neck. **B:** Chest radiograph showing the IPG within the left chest.

the FDA at large rejected the panel's recommendation, due to continued questions about the clinical data from the SANTE trial, and Medtronic continues to work with the FDA to move toward approval.

On the other hand, CE Mark approval has been granted to both VNS and Medtronic's DBS of the ANT. Therefore, patients in Europe can take advantage of either modality, depending on patient and physician preference (Table 1).

Concerning efficacy, it is difficult to compare the trials directly, given limited access to raw data and different inclusion criteria. Both DBS of the ANT and RNS show a trend toward greater seizure reduction than VNS in blinded clinical trials (40.4% and 37.9% vs 24.5% and 27.9%, respectively; Table 1). This effect disappears in the unblinded follow-ups, however, with SANTE reporting 41%, compared with 43% and 45%, respectively, in the EO3 and EO5 trials of VNS at 1 year. Responder rates (≥ 50% reduction in seizures) show conflicting results. The VNS trials reported rates of 31% and 23.4%, both significantly different than their matched, low-stimulation groups. However, the RNS trial reported a responder rate of 29%, which was comparable to VNS but not significantly different than the RNS trial's sham-treated group. That is, whereas patients had a significant decrease in seizure frequency compared with the control group, the number of patients experiencing a ≥ 50% reduction was not significantly different than the control group. The SANTE trial also had a response rate that was not significantly different than the control response.

Trial design is also a potential source of concern when attempting to compare the studies directly. The primary criticism for the EO3 and EO5 trials is that the "control" group was actually stimulated, just at a lower stimulation frequency. Therefore, strictly interpreted, the trials really only show significant benefit of one stimulation paradigm versus the other, as opposed to best medical management alone.

The SANTE and RNS trials avoid this pitfall by using sham stimulation with no current delivery. However, again, the significant comparison being made in these trials is DBS "on" in patients versus DBS "off" in patients. No data directly compare DBS versus best medical management. In all cases, this is because of the inherent difficulty in creating truly blinded surgical trials. The fact that the VNS trials required a device to be on, but firing at a low rate, is a testament to the high frequency of easily noted side effects by the patients, such as voice alteration and paresthesias. Patients in the SANTE and RNS trials, on the other hand, could be successfully evaluated in blinded fashion, even with the devices delivering no active stimuli.

A potential criticism of the SANTE trial is that, with intention-to-treat analysis, there was a sharp increase in the frequency of seizures in treated patients during the 1st month of blinded evaluation, with the model estimating a 19% difference between groups (that is, more seizures in the treated than control group).[8] However, as explained in the trial's report, this difference appears to be due to a single patient, who had 210 partial seizures in response to the on/off cycling of his DBS device during the first 3 days of stimulation. If this patient is excluded, the benefit of the DBS is more significant, but there will always be concern generated by excluding patients from final analyses. This is probably why much of the data in the SANTE trial are reported using the median, rather than the mean, because the median is less sensitive to outliers when present.

All trials restricted their analysis to patients with partial seizures and medically refractory epilepsy. Although all trials were restricted to partial seizures in patients with medically refractory disease, there are differences in inclusion criteria that might make one particular therapy more appropriate than others for particular subgroups. For example, only the VNS trials examined patients < 18

years old, so it is unclear how DBS or RNS will work in adolescent patients. However, the adolescent age group was not analyzed separately in the VNS trials, so we have no Class I evidence examining this subgroup in particular. Nevertheless, open label studies are promising, with responder rates for pediatric patients of 50%[13] to 68%.[25]

An important difference between RNS and the other therapies is that all included patients in the RNS trial were required to have 1–2 identified epileptogenic foci. We do not know how the RNS system would fare in patients with nonlocalized epilepsy or in those with a larger number of foci. This particular question was addressed more directly in the SANTE trial, in which 9.3% of the stimulated patients had diffuse or multifocal epilepsy. These patients fared well, with a 35.0% reduction in seizures compared with the control group's 14.1%, although this difference was not significant, probably due to the low number of patients within this subgroup. Neither the EO3 nor EO5 trial analyzed patients in terms of the number of epileptogenic foci, so there remains no Class I evidence for the use of VNS in this subgroup. However, unblinded trials suggest that VNS is effective in multifocal epilepsy: for example, there was a 75% seizure reduction after 3 years in one trial of adults and pediatric patients.[4] Unblinded studies also support the use of VNS in epilepsy from causes such as Lennox-Gastaut syndrome, tuberous sclerosis, postinfections, and others.[25] The data from the RNS system and DBS of the ANT are still developing, and as of yet the results have not addressed these alternative etiologies directly.

Adverse events appear to be most frequent with the use of VNS; for example, two-thirds of patients experience voice alteration, nearly half experience new cough, and one-quarter have headaches (Table 2). This compares with headaches in 3.7% of the SANTE patients and 2.6% of the RNS patients. Although depression and memory impairment were reported in both the SANTE and the RNS trials, they were more likely to occur with DBS of the ANT (14.8% and 13.0%, respectively) than with RNS (3.1% and 4.2%, respectively, over the entire 1st year). Moreover, these complaints were significantly more likely to occur in actively stimulated patients in the SANTE trial than in controls, whereas there was no difference in adverse events in controls versus patients in the RNS trial. Importantly, there were no catastrophic adverse events, such as periprocedural death, stroke, or paralysis, in any of the 4 randomized controlled trials.

Some practical considerations for these devices include battery life and implications for imaging. Because DBS of the ANT requires high stimulation currents and frequent stimulation, patients require battery replacement for their device more frequently than do those being treated with VNS (yearly in some patients with DBS of the ANT vs every several years for typical VNS-treated patients). Although all devices are compatible with low-strength (1.5-T) MRI, high-field MRI is not approved while the devices are in place. Moreover, whereas VNS generators can be safely explanted, the associated stimulation cuffs cannot be, due to adherence to the nerve. There is currently no published safety information on MRI in these patients with retained stimulation cuffs. Therefore, MRIs should be performed with extreme caution in patients with explanted VNS devices, pending further study. Because DBS leads can be fully removed, this consideration is not present for DBS of the ANT or the RNS system.

Conclusions

There are now 3 stimulation-based neuromodulation therapies for epilepsy with positive Class I evidence: VNS, DBS of the ANT, and RNS. There are no head-to-head comparisons of these therapies, but all appear to have some limited effectiveness, and all might have application for particular subgroups of patients (Table 3). Depending on which metric is used, any one of the modalities might be viewed as more efficacious than another. The device-related morbidity appears to be specific to the surgical procedure and target of stimulation. The DBS of the ANT and RNS methods have, strictly speaking, fewer adverse events than VNS, although the makeup of events is incongruous (for example, voice changes with VNS vs depression with DBS). Moreover, the intracranial implantation of DBS leads and subdural electrodes is arguably a more invasive procedure than peripheral VNS implantation.

Importantly, however, the rate of serious adverse events such as death or paralysis was < 1%–2% across all devices. Although the RNS system has fewer reported adverse events than DBS of the ANT or VNS, the RNS system is untested on multifocal or diffuse epilepsy, whereas

TABLE 3: Possible indications for neuromodulatory therapies*

Indication	Therapy		
	VNS	DBS of ANT	RNS
age			
adolescents (12–17 yrs)	likely (not specifically tested in RCTs)	?	?
adults (>18 yrs)	yes (Class I)	yes (Class I)	yes (Class I)
epilepsy type			
partial	yes (Class I)	yes (Class I)	yes (Class I)
focal (1–2 foci)	likely	likely (not specifically tested)	yes (Class I)
diffuse	likely	likely	?
generalized	?	?	?

* Question marks indicate no or inconclusive evidence. Abbreviation: RCT = randomized controlled trial.

DBS seems to have benefit, although it is not statistically significant. Similarly, unblinded trials suggest that VNS is efficacious for multifocal epilepsy; however, again, Class I evidence is lacking. Adolescent patients were included in the VNS trials, whereas RNS and DBS used only patients ≥ 18 years of age, and unblinded studies support the use of VNS in pediatric patients. We will have to await further studies to determine the effectiveness of DBS of the ANT and RNS for pediatric use. Last, only VNS is FDA approved in the US, making it the only option for most patients. In Europe, both VNS and DBS of the ANT are approved, allowing more choice for patients and physicians. However, the RNS system is under review, and DBS of the ANT is also awaiting further decision on its FDA status. In the future, as more treatments become available, comparing efficacy between stimulation modalities across the broad range of causes of epilepsy will become increasingly important. However, in any case, the advent of increasingly more sophisticated methods of treating epilepsy represents great progress in the field, and the outlook for further advancements is promising.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Chang, Rolston. Acquisition of data: Rolston. Analysis and interpretation of data: Chang, Rolston. Drafting the article: Rolston, Englot, Wang. Critically revising the article: all authors. Reviewed submitted version of manuscript: Rolston, Englot, Wang, Shih. Statistical analysis: Rolston. Administrative/technical/material support: Chang.

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